

Optimizing vaccine allocation for COVID-19 vaccines: critical role of single-dose vaccination.

Laura Matrajt,^{1*} Julia Eaton,² Tiffany Leung,¹ Dobromir Dimitrov,^{1,3}
Joshua T. Schiffer,^{1,4} David A. Swan,¹ Holly Janes¹

¹Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

² School of Interdisciplinary Arts and Sciences, University of Washington, Tacoma, USA

³ Department of Applied Mathematics, University of Washington, Seattle, WA, USA

⁴ Department of Medicine, University of Washington, Seattle, WA, USA

⁴Clinical Research Division, Fred Hutchinson Cancer Research Center, WA, USA

*To whom correspondence should be addressed; E-mail: laurama@fredhutch.org

Abstract

Most COVID-19 vaccines require two doses, and current vaccine prioritization guidelines for COVID-19 vaccines assume full-dose vaccine deployment. However in the context of limited vaccine supply and an expanding pandemic, policymakers are considering single-dose vaccination as an alternative strategy. Using a mathematical model combined with optimization algorithms, we determined the optimal allocation with one and two doses of vaccine to minimize five metrics of disease burden under various degrees of viral transmission. Under low transmission, we show that the optimal allocation of vaccine critically depends on the level of single-dose efficacy (SDE). If the SDE is high, single-dose vaccination is optimal, preventing up to 36% more deaths than a strategy prioritizing full-dose vaccination for older adults first. With low or moderate SDE, mixed vaccination campaigns with coverage of all older adults with one dose are optimal. However, with modest or high transmission, vaccinating older adults first with two doses is best, preventing up to 41% more deaths than a single-dose vaccination given across all populations. Further, we show that maintaining social distancing interventions and speedy deployment are key for effective vaccination campaigns. Our work suggests that it is imperative to determine the efficacy and durability of single-dose vaccines, as mixed or single-dose vaccination campaigns may have the potential to contain the pandemic much more quickly.

Introduction

COVID-19 has killed over 1,900,000 people worldwide as of January 15, 2021 [1]. With several vaccines proven highly efficacious (estimated at 94.1%, 95% and 62% for Moderna, Pfizer and AstraZeneca, respectively) against COVID-19 disease [2, 3, 4], hopes are high that a return to normal life can soon be possible. Twenty other vaccines are currently in phase 3 clinical trials [5]. Most of these vaccines require two doses given at least three weeks apart [6]. Since a large proportion of the global population needs to be vaccinated to reduce transmission and mortality, vaccine supply shortage will be inevitable in the first few months of vaccine availability. Even in high-income countries, which have secured the largest quantities of vaccine, supply will be initially highly insufficient [7]. This situation could be far worse in low- and middle-income countries (LMIC), where vaccine supplies might arrive at later times and in smaller quantities, with limited vaccine supply for LMIC risking the public and economic health of those populations as well as that of the global population [8].

Most of the current vaccine prioritization schedules use two-dose deployments [9], but the logistics of a two-dose vaccination campaign, which ensures a second dose for those who have already received one dose, are challenging especially in the context of limited vaccine supply and shelf-life [10]. In previous disease outbreaks, fractional dosing, where people receive less than the recommended dosage of vaccine, has been successfully utilized as a way to stretch vaccine supply. A single-dose campaign of the killed oral cholera vaccine (which also requires two doses) was deployed in a recent outbreak in Zambia, where the population was vaccinated with one dose and, months later, high-risk individuals were offered a second dose [11]. In 2016, in response to a yellow fever outbreak in Angola, Uganda and the Democratic Republic of Congo, the WHO vaccinated people with one fifth of the recommended dosage of the yellow fever vaccine [12]. If sufficiently effective, single-dose COVID-19 vaccination is attractive for several

reasons: it is easier to implement logistically, potentially less costly, and a larger proportion of the population could be vaccinated in a fixed amount of time, thereby potentially reaching herd immunity levels and allowing resumption of key community activities (e.g., reopening schools, restaurants, gyms, etc.) more rapidly [13, 14, 15]. This may be especially true if vaccines reduce not only COVID-19 disease but also reduce acquisition of SARS-CoV-2 infection and the likelihood of onward transmission; these are open questions and data are still emerging on the full spectrum of vaccine effects [16, 3]. However, the success of a COVID-19 single-dose vaccination campaign depends on the protection acquired after one dose of vaccine. There is an intrinsic trade-off with using single-dose vaccination campaigns to achieve more coverage in exchange for a potentially lower level of protection. In this work, we addressed two questions of public-health importance: 1. Who should be vaccinated first? and 2. How many doses should individuals receive? Utilizing mathematical models combined with optimization algorithms, we determined the optimal allocation of available vaccine doses under a variety of assumptions. We minimized five metrics of infection and disease burden: cumulative infections, cumulative symptomatic infections, cumulative deaths, and peak non-ICU and ICU hospitalizations. We showed that mixed vaccination strategies in which some age groups receive one dose while others receive two doses can achieve the greatest reduction in these metrics under fixed vaccine quantities. Further, our results suggest that the optimal vaccination strategy depends on the relative efficacy of single- vs. full-dose vaccination; on the full spectrum of vaccine effects; on the number of vaccine doses available; and on the speed of vaccine rollout and the intensity of background transmission.

Results

We built upon our previous model of SARS-CoV-2 dynamics and vaccination [17]. Briefly, we developed an age-structured mathematical model with the population of Washington state (7.6

million people) and US demographics divided into 16 age-groups [18] (Fig. S1). To perform the vaccine optimization, we collapsed the 16 age-groups into 5 vaccination age-groups: 0–19, 20–49, 50–64, 65–74 and those 75 and older, aligned with vaccination groups currently considered by the Centers for Disease Control and Prevention (CDC) [19]. We assumed that at the beginning of our simulations, 10% of the population has been infected and is immune [20] (alternative scenario: 20% see Sensitivity Analysis, SI). We assumed that asymptomatic and symptomatic infections are equally infectious (alternative scenario: Sensitivity Analysis, SI) and confer complete immunity upon recovery. Further, we assumed that both naturally-acquired immunity and vaccine-induced immunity (one- and two-dose) are long-lasting, so that there is no waning during the time period analyzed.

Because it is expected that vaccine supplies will ramp up considerably over the second half of 2021 and into 2022, we focused on the first few months of vaccine availability and set 6 months for the duration of our simulations. We considered the distribution of enough vaccine doses to cover from 10% to 50% of the population with a single dose. We simulated vaccination campaigns delivering 150,000 (150K) vaccine doses per week, with a maximum of 50% of the population vaccinated with a single dose of vaccine over a ~6-month period (our time horizon). This matches current vaccination plans in the US [21]. An alternative scenario with 300K vaccine doses per week was also explored. These are roughly twice and four times, respectively, the vaccination rate experienced in the US during the 2009 H1N1 influenza pandemic [22].

We considered four levels of background SARS-CoV-2 transmission, resulting in an effective reproductive number (defined as the average number of secondary cases per infectious case in a population made up of both susceptible and non-susceptible hosts) of $R_{\text{eff}} = 1.2, 1.4$, (currently observed in WA state, [23]), 1.7 or 3 that was kept constant over time. We assumed that front-line workers (e.g., healthcare workers, firefighters), who should be prioritized, have already been vaccinated, and they are not explicitly modeled here. We evaluated five metrics

of disease and healthcare burden: cumulative infections, cumulative symptomatic infections, cumulative deaths, maximum number of non-ICU hospitalizations and maximum number of ICU-hospitalizations. State goals for limiting hospital and ICU beds occupied by COVID-19 patients [24, 25] were used for result interpretation.

Ongoing phase 3 COVID-19 vaccine trials evaluate vaccine efficacy against laboratory-confirmed COVID-19 disease, or the multiplicative reduction in per-exposure risk of disease which we denote by VE_{DIS} . We considered a leaky vaccine (that is, a vaccine that confers partial protection to all vaccinated individuals) that can have three effects on vaccinated individuals [26]: reducing the probability of acquiring a SARS-CoV-2 infection (measured by VE_{SUS}), reducing the probability of developing COVID-19 symptoms after infection (measured by VE_{SYMP}), or reducing the infectiousness of vaccinated individuals upon infection (measured by VE_I , Fig. S2A).

Given the efficacy data on two-dose COVID-19 vaccines to date [2, 3, 4], we considered a main scenario with $VE_{DIS} = 90\%$. Because many combinations of VE_{SUS} and VE_{SYMP} can result in the same VE_{DIS} (Fig. S2B), and in advance of definitive data on VE_{SUS} or VE_{SYMP} for COVID-19 vaccines, we considered three different vaccine profiles that yield $VE_{DIS} = 90\%$: a vaccine effect mediated by VE_{SUS} only, a vaccine effect mediated by VE_{SYMP} only, and a vaccine effect that is a combination of VE_{SUS} and VE_{SYMP} (Fig. S2B, table S1). In the absence of data on the vaccine effect on infectiousness, we took a conservative approach and assumed $VE_I = 0$ (alternative scenario, $VE_I = 70\%$, Sensitivity Analysis, SM). Given the limited data to-date regarding the efficacy of single-dose vaccination, we considered three “single-dose efficacy” (SDE) scenarios, under our main scenario where two-dose $VE_{DIS} = 90\%$: low SDE, whereby the single-dose vaccine confers low efficacy against COVID-19 disease ($VE_{DIS_1} = 18\%$); moderate SDE with $VE_{DIS_1} = 45\%$; and high SDE with $VE_{DIS_1} = 72\%$; corresponding to 20, 50, and 80% of the 90% efficacy of the full two-dose regimen, respectively. The efficacy of single-dose

vaccination against infection and symptoms were assumed to be reduced proportionally. All vaccine effects were assumed to take effect immediately following the last vaccination and to be constant over the time horizon of 6 months. For two dose vaccination, we explicitly modeled vaccination campaigns with the first dose, followed by vaccination campaigns with the second dose, so that individuals receiving two doses had the protection conferred by single dose vaccination in the inter-vaccination period.

Throughout the text, we refer to vaccine coverage as the amount of vaccine available to cover a percentage of the population with one dose of vaccine. For each vaccination scenario and disease metric, we compared the *optimal allocation strategy* that minimized the respective disease metric (as determined by our optimization routine) to two other strategies: a *pro-rata strategy* in which one-dose vaccination is rolled out across all age groups proportional to their size; and a *high-risk strategy* in which two-dose vaccination is rolled out to the oldest age group first and then to younger age groups in decreasing order as vaccine availability permits (similar to the current prioritization strategy in the US [27]). For example, with 20% coverage, under the *pro-rata strategy* 20% of each group would receive a single dose of vaccine, and under the *high-risk strategy* all people aged 75 and older and 32% of those aged 65 to 74 years would receive two doses of vaccine (Fig. S3)A.

In the main scenario, we considered a vaccine mediated both by VE_{SUS} and VE_{SYMP} , so that $VE_{DIS} = 90\%$ after two doses with $VE_{SUS} = 70\%$ and $VE_{SYMP} = 66\%$, a vaccination campaign with 150K doses per week, and $R_{eff} = 1.4$, focusing on minimizing COVID-19 deaths.

Single dose vaccination strategies are optimal if SDE is high. If a limited number of vaccine doses are available ($\leq 20\%$ coverage) then for all metrics considered, the *optimal strategies* allocated vaccines to children and younger adults (who are the high-transmission groups in our model), regardless of the efficacy of a single dose (Fig. 1A-F and Fig. S4).

If SDE was low or moderate combined with low coverage, the *optimal strategies* allocated two doses of vaccine to the high-transmission groups (Fig. S3A and B), averting up to 45 and 25% more deaths compared to the *high-risk* and *pro-rata strategies* (low SDE, 20% coverage, Fig. 2D and E). This is because at low coverage, the most effective strategy is to reduce the transmission as much as possible, and this is achieved by prioritizing vaccination of the most active groups (Fig. S3D and E). For higher coverage (30–50%), mixed allocation strategies were optimal, vaccinating all age groups with two doses and additionally vaccinating older adults with a single dose to boost their coverage (Fig. 1G, H, J, K, M and N). For example, with 50% coverage, 25, 20, 10, 10, and 28% of each age group was vaccinated with two doses, and an additional 19, 32 and 47% of the 50–65, 65–75 and 75+ were vaccinated with a single dose (Fig. 1M). Here, the *optimal strategy* averted up to 40% more deaths than the *pro-rata strategy*, but performed similarly to the *high-risk strategy* (9% more deaths averted for 30% coverage and moderate SDE, Fig. 2D and E).

In sharp contrast, if a single dose of vaccine was highly efficacious, then, for all metrics considered, the *optimal strategies* involved vaccinating individuals with one dose of vaccine almost exclusively (Fig. 1, Figs. 3 and S4 panels C, F and I). If the vaccine supply was limited (up to 20% coverage), it was optimal to allocate a single dose of vaccine to the high-transmission groups, averting up to 36 and 11% more deaths than the *high-risk* and *pro-rata strategies* (10% coverage, Fig. 2F). For higher coverage (30–50% coverage) the *pro-rata strategy* was in fact optimal (Fig. 4C), averting 13–26% more deaths than the *high-risk strategy*. If sufficient doses of high SDE vaccine were available to ensure 50% coverage, this strategy significantly mitigated the epidemic by preventing 78% of the expected COVID-19 deaths over 6 months (compared with no vaccination, Fig. 4F).

Different metrics have different optimal allocation strategies. Minimizing other metrics of disease and healthcare burden produced different optimal allocation strategies. With low coverage, regardless of the value of the SDE, the optimal allocation was similar across metrics with all vaccine doses was designated to the high-transmission groups (children and young adults) (Fig. S4). With higher coverage and high SDE, it was best to allocate vaccine to high-transmission groups to minimize transmission (cumulative infections and symptomatic infections, Fig. 3C and F), but it was best to allocate vaccine with a *pro-rata strategy* to minimize severe disease outcomes (hospitalizations and deaths, Fig. 3I, L, O). Notably, with 50% coverage, the *optimal* and the *high-risk* strategies maintained the number of peak ICU hospitalizations below total capacity, but only the *optimal strategy* achieved the Washington state goal for non-ICU peak hospitalizations (Fig. S5 and Fig. S6).

Rapid vaccination roll-out under sustained social distancing is key for successful vaccination campaigns. We investigated the effect of SARS-CoV-2 transmission on optimal allocation strategies. Under stringent social distancing interventions maintaining $R_{\text{eff}}=1.2$, the efficacy after a single dose determined the optimal allocation strategy. With low or moderate SDE and low coverage, it was optimal to vaccinate high-transmission groups with two doses. If SDE was low, the *optimal strategy* averted 34 and 35% more deaths than the *high-risk* and *pro-rata* strategies respectively (10% coverage, Fig. 2A). With higher coverage, mixed strategies were optimal, with adults aged 50–74 being vaccinated in a higher proportion with a single dose (Fig. 5A, B, D, and E); with 50% coverage, the *optimal strategy* averted 12% and 40% more deaths than *high-risk* and *pro-rata* strategies respectively (Fig. 2B). If the SDE was moderate, the *optimal strategy* averted 35 and 18% more deaths than the *high-risk* and *pro-rata* strategies at low coverage, but only averted an additional $\sim 12\%$ more deaths than the other two strategies at high coverage. In contrast, if the vaccine had high SDE, the *pro-rata strategy* was

in fact optimal for all coverages, averting additional 40% deaths than the *high-risk strategy* at low coverage and 18% at high coverage (Fig. 5C and F, Fig. 2C).

If viral transmission was moderate or high ($R_{\text{eff}}=1.7$ or 3), then the *high-risk strategy* was the optimal use of vaccine especially for scenarios with low and moderate SDE, where it averted up to 41% more deaths than the *pro-rata strategy* ($R_{\text{eff}}=1.7$, 40% coverage and low SDE, Fig. 5 and Fig. 2G, H, J, K). For high SDE, the *optimal strategy* was still to vaccinate the high-risk groups first, but using mixed vaccination (with one and two doses). For example, with enough vaccine to cover 50% of the population and a vaccine with a high SDE, it was optimal to cover all adults aged 65 and over with two doses and those aged 50–64 with a single dose of vaccine with the remaining vaccine supply (Fig. 5I and L). However, the gain from optimizing vaccine allocation to improve *high-risk strategy* was relatively small at low coverage (10% more deaths averted with 20% coverage), but averted up to 20% more deaths than the *pro-rata strategy* (10% coverage, $R_{\text{eff}}=3$). All strategies performed similarly for high coverage (Fig. 2I and L).

Regardless of the SDE, for all levels of viral transmission considered, the epidemic advanced at a faster pace than the vaccination campaign, evidenced by the fact that the percentage of deaths averted plateaued at 40% ($R_{\text{eff}}=1.2$) and 30% coverage ($R_{\text{eff}}=1.4$, 1.7 and $R_{\text{eff}}=3$), Fig. 2. Notably, in controlled epidemic settings ($R_{\text{eff}}=1.2$ and 1.4) the optimized strategies allow for reaching the ceiling of the vaccination impact much faster with significantly fewer vaccine doses.

The vaccine profile shapes the optimal allocation strategy. In this section we analyzed how different vaccine profiles affected the optimal allocation strategies. With a vaccine effect on COVID-19 disease mediated by a reduction in symptoms (high VE_{SYMPT}), the optimal strategies for minimizing deaths allocated two doses of vaccine to older adults (aged 65 and older)

for direct protection (Fig. 6A-C). If the reduction in disease was mediated by both a reduction in SARS-CoV-2 infection and in symptoms (high VE_{SYMP} and VE_{SUS}), or predominately by preventing infection (VE_{SUS}), then mixed strategies allocating more vaccine doses to older adults are optimal for a low or moderate SDE while the *pro-rata strategy* was optimal if the SDE was high (Fig. 6D-I).

The vaccine efficacy profile had little effect on mortality prevented by the *high-risk strategy* (regardless of the SDE) but a major effect on the *pro-rata strategy* impact: while this allocation performed very poorly if the vaccine was mediated by VE_{SYMP} and low SDE, it was extremely effective if the vaccine was mediated also by VE_{SUS} and had a high SDE (Fig. S7). A vaccine preventing only symptomatic disease has the potential to prevent only up to 62% of deaths over 6 months compared to 86% reduction in mortality if exclusively mediated by preventing infection (Fig. S7C and I). Moderate protection against infection (VE_{SUS}) was important to all vaccination strategies to ensure reduction in transmission but especially for the *optimal strategy* (Fig. S8). A vaccine acting exclusively by reducing symptomaticity had no impact on the overall transmission (maximum of 4% of cumulative infections averted, Fig. S8A-C) while a vaccine that reduced SARS-CoV-2 acquisition could, if optimally allocated, avert 97% of cumulative infections (Fig. S8I).

Sensitivity analysis

Results assuming asymptomatic infections are less infectious: Simulations assuming that asymptomatic infections are 50% less infectious than symptomatic infections showed similar results. The optimal allocation strategies in this scenario depended mostly on the SDE, notably: i) the *pro-rata strategy* was optimal for high SDE and high coverage and ii) single-dose vaccination of the high transmission groups was the *optimal strategy* with low coverage (Fig. S9). As expected, if asymptomatic infections are less infectious, then a vaccine mediated exclusively by

reducing symptomatic disease does have a significant impact in overall transmission, preventing as much as 66% of total infections (50% coverage, high SDE, Fig. S10). Furthermore, under this scenario, such a vaccine would avert slightly more deaths (a maximum of 67% averted deaths vs 63% in the main scenario).

Results assuming 20% cumulative incidence at the start of vaccination: We repeated the main analysis assuming 20% of the population has been infected and therefore immune at the beginning of vaccination. Again, the results were consistent with the main scenario, with optimal vaccination strategies favoring single-dose campaigns if the SDE is high (Fig. S11). In this scenario, the epidemic grows very slowly even in the absence of vaccine with only the exponential phase of the epidemic curve observed toward the end of the simulations. This is because with 20% of the population already immune and the assumed reduction in contacts resulted in an much lower R_{eff} ($R_{\text{eff}}=1.2$). As a result, the projected impacts of different strategies are very similar to the ones presented above with $R_{\text{eff}}=1.2$ with *optimal strategy* outperforming the other strategies for low and moderate SDE and *pro-rata strategy* being optimal for high SDE (Fig. S12).

Results assuming more rapid vaccine delivery: We next investigated the effect of vaccination rate in the optimal allocation strategies. Here, we assumed that vaccine was rolled out at 300K doses per week (twice as fast as main scenario). At this rate, 100% of the population can be vaccinated with a single dose in the same time period. With low coverage, the *optimal strategy* was identical to the one described in the main scenario. With high coverage, the *optimal strategy* differed only for low and moderate SDE, by allocating even more vaccine with two doses to the high-transmission groups (Fig. S13D, E). With enough vaccine to cover 50% of the population and administering 300K doses per week the *optimal strategy* averted

17% more deaths compared to one distributing 150K doses per week (95% and 78% the deaths averted compared with no vaccination, vaccinating at 300K and 150K doses per week respectively, Figs. S13C and 4E). Furthermore, at this rate, the *optimal strategy* significantly mitigates transmission even with low and moderate SDE, and temporary herd immunity is achieved if the vaccine has a high SDE (Fig. S13G-I).

Results assuming vaccine efficacy in reducing infectiousness upon infection: We identified the optimal allocation strategies assuming that a vaccine, in addition to all the effects previously described ($VE_{DIS} = 90\%$ after two doses with $VE_{SUS} = 70\%$ and $VE_{SYMP} = 66\%$) also reduces infectiousness upon infection by 70% ($VE_I = 70\%$) after two doses. For low and high SDE and for all coverage levels considered, the *optimal strategies* were very similar to the ones previously described. For moderate SDE the optimal allocation suggested more single dose vaccination of the high-transmission groups at low coverage, and mixed vaccination of all age groups for high coverage, reducing the focus on older age groups (Fig. S14). As expected, all vaccination strategies averted more deaths due to additional vaccine effects on infectiousness. With 50% coverage, the *optimal strategies* averted 10% more deaths compared to the main scenario, regardless of the SDE (74, 80 and 88% deaths averted for low, moderate and high SDE in this scenario vs. 64, 69 and 78% deaths averted for the main scenario, Figs. 4 and S15 panels A-C).

Discussion

COVID-19 vaccination has begun in several countries, and more countries will start in the upcoming months. As demand will far exceed supply in the initial months of vaccine deployment, vaccine will need to be prioritized. Most of the current strategies consider vaccination with full dosage (two doses), but some countries have proposed vaccinating twice as many people with

a single dose (and delaying the second dose) [28]. An intense debate about how best to use the available vaccine is ongoing [13, 29, 30]. Here, we show that there is no universal answer to this question. Pairing a mathematical model parameterized using the evidence to-date on the efficacy of COVID-19 vaccines with optimization algorithms, we explore the use of single-dose campaigns and mixed vaccination campaigns, with some people receiving one dose and others receiving two doses, and we find that the optimal use of resources depends primarily on the level of single-dose efficacy, in agreement with [15]. If a single dose of vaccine is highly efficacious and introduced under stringent social distancing interventions with low viral transmission, our results suggest that campaigns that optimally distribute a single vaccine dose to more people are far more effective at averting deaths than a two-dose vaccination campaign prioritizing subpopulations at high risk of COVID-19 severe disease and death. Previous work for other infectious diseases [31, 32, 33] has reached similar conclusions. Furthermore, our results show that vaccinating with a single-dose at a faster rate could result in temporary herd immunity, in agreement with previous work [34]. As more vaccine becomes available, additional vaccination campaigns will be needed to cover everyone with the full two doses of vaccine. However, in places where SARS-CoV-2 transmission is moderate or high ($R_{\text{eff}}=1.7$ or 3 in our model), a two-dose campaign from the outset is optimal.

In addition, we show that optimal distribution of available vaccine doses across subpopulations depends strongly on the level of transmission. If the ongoing transmission in the community is well controlled with stringent non-pharmaceutical interventions in place, the *optimal strategy* allocated vaccine to the high-transmission groups, consistent with previous work [35]. If the transmission is moderate or high, it is optimal to directly protect those at higher risk of severe disease and death, also in agreement with previous results [36, 17]. Our analysis reiterates the absolute necessity of maintaining social distancing throughout vaccination [37, 38, 39]: if social distancing interventions are lax before vaccination is advanced, or if vaccination is not

rolled out fast enough, then the current epidemic wave will be over long before vaccination campaigns are completed and the effect of vaccination will be limited.

While high vaccine efficacy against COVID-19 disease has been reported for the two licensed vaccines (Pfizer and Moderna), other effects of COVID-19 vaccines require further evaluation, including their effects on preventing SARS-CoV-2 infection and on infectiousness. To account for these gaps in knowledge, we investigated the optimal vaccine allocation under three possible vaccine profiles consistent with the observed vaccine efficacy against disease, and we found that the optimal vaccination strategy depends on the profile. Our analysis showed that a vaccine which mostly mitigates symptoms but does not reduce the risk of infection should be prioritized to the oldest age groups at full dosage. In contrast, the optimal strategy for a vaccine which provides at least moderate protection against infection includes more balanced dose distribution across age groups with larger proportions assigned to one-dose vaccinations. Similar to [39], we found that a vaccine that only prevents disease upon infection will have limited population impact, whereas a vaccine preventing infection will both reduce population transmission and subsequent morbidity and mortality. These results underscore the need for thorough studies to evaluate all of the vaccine effects.

Beyond the impact on infection and disease burden, there are additional arguments for considering single-dose vaccination, including greater equity achieved in distributing a scarce commodity (vaccine) [13], reduced reactogenicity following the first versus the second dose of the mRNA vaccines [16, 3], and the potential for greater population uptake and adherence to a single-dose regimen. Policy-makers would ideally consider these issues in evaluating possible vaccination strategies.

Here, we report the optimal use of resources as determined by mathematical optimization. In practice, other factors (ethical, political, logistical, etc.) need to be considered when allocat-

ing vaccine. We quantified the advantages and disadvantages of two policies that closely mimic current guidelines—pro-rata vaccination and vaccination of groups at high risk of disease—and identified when either of these coincides with our computed optimal allocation strategy, or achieves similar public health impact. While optimal allocation strategies may be difficult to implement, our results can be used to guide the development of mixed vaccination strategies, where some subpopulations receive one dose and others receive two doses, thereby achieving a balance between rapid coverage and full protection of those most at risk of severe disease and death.

Our work has several limitations. Our model assumed that asymptomatic and symptomatic infections confer equal protection, but asymptomatic infections could result in weaker protection [40]. We assumed that naturally and vaccine-induced immunity will be long-lasting, but some studies suggest that it might last only a few months [41]. Ongoing phase 3 trials will establish the durability of vaccine efficacy, with participants followed 1 to 2 years post-last vaccination. If immunity is short-lived, then our results are valid only for that time frame. We also assumed that vaccinating previously infected individuals would have no effect on their immunity. However, it is possible that previous infections might act as a first dose of vaccine and that vaccinating those individuals might result in a boost of their immunity. We use age-stratified hospitalization rates based on data from Wuhan, China [42] and mortality rates based on data from France [43]. These rates strongly depend on comorbidities (e.g., heart disease, diabetes, etc.) that are country-dependent. It is then important to determine country-based estimates of these rates to adequately parameterize models. For mathematical and computational tractability, we used a deterministic model that does not account for geographic movement or complex contact patterns and age was our sole risk factor. In reality, we know that other factors, such as occupation, have been linked to an increased risk of acquisition and severe disease [44, 45]. Be-

cause of systemic social inequalities, several studies have shown that in certain countries people from racial and minority groups are at increased risk of infection and death from COVID-19 [46]. Further, deterministic models can overestimate infection dynamics. While comparisons with and without vaccination strategies would not be affected by this, it is possible that our peak hospitalizations are overestimated. We kept the effective reproductive number (and hence viral transmission) constant throughout the simulations. However, social distancing interventions are being constantly changed and adapted to new challenges when transmission is high. We included children in our analysis, but vaccines are not currently licensed for individuals under 16 years old. However, studies are currently undergoing for the AstraZeneca and Pfizer vaccines including children 12 years old and older [47] and studies in children for other vaccines are being planned, so it is possible that one or more COVID-19 vaccines will be licensed in children within the next 6 months. Finally, we have determined optimal allocation strategies in the context of considerable uncertainty as to COVID-19 vaccine profiles and vaccine rollout; once profile, vaccination rates and coverages for specific countries are known, we welcome validation with more complex models.

There are reports of new and more transmissible SARS-CoV-2 variants originating from the UK and South Africa that are spreading rapidly and circulating in several parts of the globe. It is still unknown how efficacious currently available vaccines will be against these variants [48, 49]. A potential concern with single-dose vaccination is that vaccinating large numbers of people with a regimen with suboptimal efficacy may allow selection to drive the emergence of new vaccine-resistant variants that can rise rapidly in frequency [50].

While limited data suggest that a single dose of the three COVID-19 vaccines with regulatory licensure or approval in the US and UK might confer high efficacy [2, 3, 51], the data are

preliminary and the duration of protection is unknown. Other vaccines that require two doses, such as the oral cholera vaccine, are highly effective after a single dose but the protection provided is short-lived compared to that provided by the full two-dose regimen [52]. If single-dose immunity lasts for at least 6 months, our results show that single-dose vaccination campaigns, which are much easier to implement, are the optimal use of resources in the short term, with the goal to fully vaccinate the entire population in the long term. In the absence of phase 3 efficacy data on single-dose vaccination, it will be crucial for vaccine safety systems to capture any breakthrough infections that occur among individuals receiving vaccination under population campaigns—especially those receiving a single dose; and for longitudinal immune responses to be measured in clinical trial participants who received only one dose. Our work suggests that it is an absolute imperative to quickly and fully determine the peak and duration of efficacy of single-dose vaccinations, as these data are needed to support further investigation of mixed vaccination campaigns which have great potential to more quickly contain the pandemic.

References

- [1] Johns Hopkins University and Medicine, Coronavirus COVID-19 global cases by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) (2020).
- [2] FDA, FDA Briefing Document, Moderna COVID-19 Vaccine, <https://www.fda.gov/media/144434/download> (2020). last accessed Dec 27th, 2020.
- [3] F. P. Polack, *et al.*, *New England Journal of Medicine* (2020).
- [4] M. Voysey, *et al.*, *The Lancet*.
- [5] J. Corum, D. Grady, S.-L. Wee, C. Zimmer, Coronavirus Vaccine Tracker (2020).

- [6] STAT, A side-by-side comparison of the Pfizer/BioNTech and Moderna vaccines, <https://www.statnews.com/2020/12/19/a-side-by-side-comparison-of-the-pfizer-biontech-and-moderna-vaccines/> (2020). last accessed, Dec 27th, 2020.
- [7] The Economist, Rich countries grab half of projected covid-19 vaccine supply (2020).
- [8] WHO, Global equitable access to COVID-19 vaccines estimated to generate economic benefits of at least US\$ 153 billion in 2020–21, and US\$ 466 billion by 2025, in 10 major economies, according to new report by the Eurasia Group, <https://www.who.int/news/item/03-12-2020-global-access-to-covid-19-vaccines-estimated-to-generate-economic-benefits-of-at-least-153-billion-in-2020-21> (2020). last accessed Jan 14th, 2021.
- [9] NAS, Final Report Public Release Webinar: Framework for Equitable Allocation of COVID-19 Vaccine, <https://www.nationalacademies.org/event/10-02-2020/final-report-public-release-webinar-framework-for-equitable-allocation-of-covid-19-vaccine> (2020). last accessed Dec 27th, 2020.
- [10] B. Lovelace Jr., The U.S. has vaccinated just 1 million people out of a goal of 20 million for December, <https://www.cnbc.com/2020/12/23/covid-vaccine-us-has-vaccinated-1-million-people-out-of-goal-of-20-million-for-december.html> (2020). last accessed Dec 27th.
- [11] E. Ferreras, *et al.*, *New England Journal of Medicine* **378**, 577 (2018). PMID: 29414267.
- [12] WHO, Yellow fever mass vaccination campaign using fractional dose in Kinshasa, DRC, http://www.who.int/immunization/sage/meetings/2016/october/4_Yellow_fever_mass_vaccination_campaign (2016).

- [13] R. V. Barnabas, A. Wald, *Annals of Internal Medicine* (2021).
- [14] A. D. Paltiel, A. Zheng, J. L. Schwartz, *Annals of Internal Medicine* pp. 1–2 (2021).
- [15] A. R. Tuite, L. Zhu, D. N. Fisman, J. A. Salomon, *Annals of Internal Medicine* (2021).
- [16] L. R. Baden, *et al.*, *New England Journal of Medicine* (2020).
- [17] L. Matrajt, J. Eaton, T. Leung, E. R. Brown, *Science Advances*, *forthcoming* (2021).
- [18] K. Prem, A. R. Cook, M. Jit, *PLoS Computational Biology* **13**, e1005697 (2017).
- [19] CDC, COVID-19 Pandemic Planning Scenarios.
- [20] Y. Gu, COVID-19 Projections Using Machine Learning, <https://covid19-projections.com/> (2020). last accessed Jan 13th, 2021.
- [21] NPR, Biden Vows To Distribute 100 Million COVID-19 Vaccine Doses In His First 100 Days, <https://www.npr.org/2021/01/08/955005344/biden-vows-to-distribute-100-million-covid-19-vaccine-doses-in-his-first-100-day> (2021). last accessed Jan 8th, 2021.
- [22] Centers for Disease Control and Prevention, Final estimates for 2009-10 seasonal influenza and influenza A (H1N1) 2009 monovalent vaccination coverage - United States, August 2009 through May, 2010 (2010).
- [23] Washington State Department of Health, COVID-19 transmission across Washington State, https://www.doh.wa.gov/Portals/1/Documents/1600/coronavirus/data-tables/WA-COVID19-Situation-Report-23_820-114.pdf (2020). last accessed Jan 11th, 2021.
- [24] Washington State Coronavirus Response, COVID-19 risk assessment dashboard (2020).
- [25] State of California, COVID-19 data and tools (2020).

- [26] M. E. Halloran, C. J. Struchiner, I. M. Longini, *American Journal of Epidemiology* **146**, 789 (1997).
- [27] Centers for Disease Control and Prevention, When Vaccine is Limited, Who Gets Vaccinated First?, <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations.html> (2020). last accessed Dec 29th, 2020.
- [28] The Guardian, Covid-19 second-stage vaccinations to be delayed across UK, <https://www.theguardian.com/world/2020/dec/30/covid-19-second-stage-nhs-vaccinations-delayed-across-uk> (2020). last accessed Jan 12th, 2021.
- [29] J. P. Moore, John P. Moore: How do you take your vaccine—one lump or two?, <https://blogs.bmj.com/bmj/2021/01/06/john-p-moore-how-do-you-take-your-vaccine-one-lump-or-two/> (2021). last accessed Jan 12th, 2021.
- [30] H. Ledford, How can countries stretch COVID vaccine supplies? Scientists are divided over dosing strategies, <https://www.nature.com/articles/d41586-021-00001-6> (2021). last accessed Jan 12th, 2021.
- [31] A. S. Azman, *et al.*, *PLoS Med* **12**, e1001867 (2015).
- [32] L. Matrajt, T. Britton, M. E. Halloran, I. M. L. Jr., *Epidemics* **13**, 17 (2015). PMID: PMC4664891.
- [33] S. Riley, J. T. Wu, G. M. Leung, *PLoS Medicine* **4**, e218 (2007).
- [34] R. M. Anderson, C. Vegvari, J. Truscott, B. S. Collyer, *The Lancet* **396**, 1614 (2020).
- [35] J. H. Buckner, G. Chowell, M. R. Springborn, *medRxiv* (2020).
- [36] K. M. Bubar, *et al.*, *medRxiv* (2020).

- [37] A. B. Hogan, *et al.*, Report 33 - Modelling the allocation and impact of a COVID-19 vaccine, <https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-33-vaccine/> (2020). last accessed Dec 27th, 2020.
- [38] S. M. Moghadas, *et al.*, *medRxiv* (2020).
- [39] D. A. Swan, *et al.*, *medRxiv* (2020).
- [40] Q.-X. Long, *et al.*, *Nature Medicine* (2020).
- [41] P. G. Choe, *et al.*, *Emerging Infectious Diseases* **27**, 327 (2021).
- [42] N. M. Ferguson, *et al.* (2020).
- [43] H. Salje, *et al.*, *Science* **369**, 208 (2020).
- [44] Centers for Disease Control and Prevention, Assessing Risk Factors for Severe COVID-19 Illness (2020).
- [45] European Centre for Disease and Prevention and Control, COVID-19 clusters and outbreaks in occupational settings in the EU/EEA and the UK (2020).
- [46] B. Seligman, M. Ferranna, D. E. Bloom, *PLOS Medicine* **18**, e1003490 (2021).
- [47] FDA, Vaccines and related biological products advisory committee December 10, 2020 meeting announcement (2020).
- [48] M. H. Cheng, J. M. Krieger, B. Kaynak, M. Ardit, I. Bahar, *bioRxiv* (2021).
- [49] X. Xie, *et al.*, *bioRxiv* (2021).
- [50] STAT, <https://www.statnews.com/2021/01/04/britain-takes-a-gamble-with-covid-19-vaccines-upping-the-stakes-for-the-rest-of-us/>,

- <https://www.statnews.com/2021/01/04/britain-takes-a-gamble-with-covid-19-vaccines-upping-the-stakes-for-the-rest-of-us/> (2021). last accessed Jan 12th, 2021.
- [51] AstraZeneca, AZD1222 vaccine met primary efficacy endpoint in preventing COVID-19, <https://www.astrazeneca.com/media-centre/press-releases/2020/azd1222h1r.html> (2020). last accessed Dec 28th, 2020.
- [52] F. Qadri, *et al.*, *The Lancet Infectious Diseases* **18**, 666 (2018).
- [53] S. A. Lauer, *et al.*, *Annals of Internal Medicine* (2020).
- [54] J. Zhang, *et al.*, *Science* **8001**, 1 (2020).
- [55] W. E. Wei, *et al.*, *Morbidity and Mortality Weekly Report* **69**, 411 (2020).
- [56] Z. Du, *et al.*, *Emerging Infectious Diseases* **26**, 1341 (2020).
- [57] Q. Bi, *et al.*, *Lancet Infectious Diseases* (2020).
- [58] Y.-H. Lee, C. M. Hong, D. H. Kim, T. H. Lee, J. Lee, *Emerging Infectious Diseases* **Oct** (2020).
- [59] K. Mizumoto, K. Kagaya, A. Zarebski, G. Chowell, *Euro Surveillance* **25** (2020).
- [60] J. Zhang, *et al.*, *The Lancet Infectious Diseases* **20**, 793 (2020).
- [61] J. T. Wu, K. Leung, G. M. Leung, *Lancet* **395**, 689 (2020).
- [62] S. Zhao, *et al.*, *International Journal of Infectious Diseases* **92**, 214 (2020).
- [63] United States Census Bureau, Washington (2020).
- [64] Population Pyramid, Population of United States of America 2020 (2020).

- [65] D. V. Mehrotra, *et al.*, *Annals of Internal Medicine* (2020).
- [66] C. Audet, W. Hare, *Derivative-Free and Blackbox Optimization* (Springer, Cham, Switzerland, 2017).
- [67] The Sage Developers, SageMath, the Sage Mathematics Software System (Version 9.1) (2020).
- [68] S. Kotz, N. Balakrishnan, N. L. Johnson, *Continuous Multivariate Distributions. Volume 1: Models and Applications* (Wiley, 2000).
- [69] F. Gao, L. Han, *Computational Optimization and Applications* **51**, 259 (2012).
- [70] P. Virtanen, *et al.*, *Nature Methods* **17**, 261 (2020).

Acknowledgements

We thank Peter Gilbert, Dimitri Leemans, and Natalia García-Colín for helpful discussions.

Funding: LM was supported by Fred Hutchinson Cancer Research Center discretionary funds awarded to Peter Gilbert and to the Scientific Computing Infrastructure at Fred Hutch funded by ORIP grant S10OD028685. HJ was supported by R56AI143418 and R01CA152089 from the National Institutes of Health. DD, JTS and DAS were supported by NU38OT000297-02 from Centers for Disease Control and Prevention. **Author contributions:** LM conceived the study, conducted the analysis and wrote the first draft of the manuscript. JE assisted with the optimization, analysis, figures and wrote the manuscript. TL, DD, JTD, DAS and HJ contributed to writing the manuscript. **Competing interests:** The authors declare no competing interests. **Data availability:** Code available upon request.

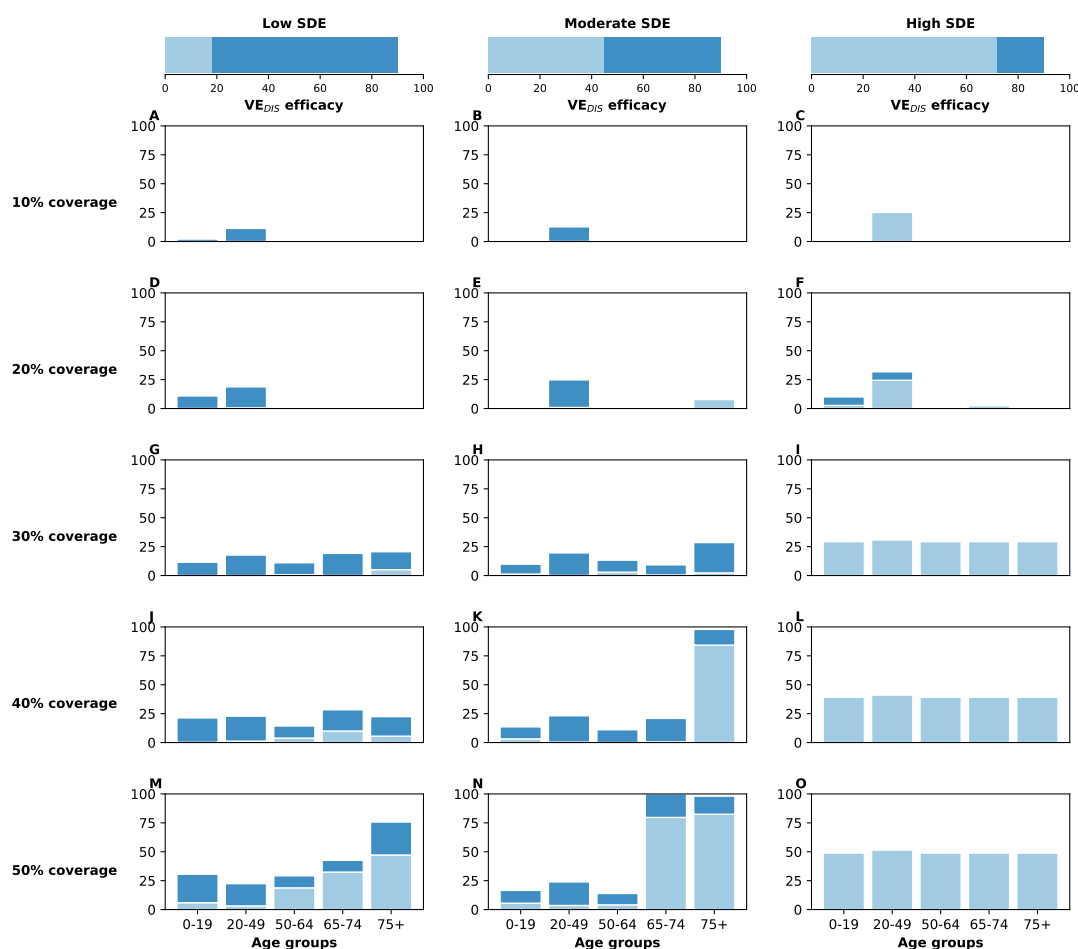


Figure 1: Optimal vaccine allocation strategies for minimizing deaths for different vaccination coverages. For each plot, the bars represent the percentage of each age group vaccinated with a single dose (light blue) and two-doses (dark blue) when there is enough vaccine to cover 10% to 50% (as indicated by row) of the population with a single dose. The columns correspond to assumptions that the single-dose efficacy (SDE) is low (left column, $VE_{DIS1} = 18\%$), moderate (center column, $VE_{DIS1} = 45\%$) or high (right column, $VE_{DIS1} = 72\%$), corresponding 20, 50 or 80% of the 90% efficacy that is assumed following two doses of vaccine, respectively.

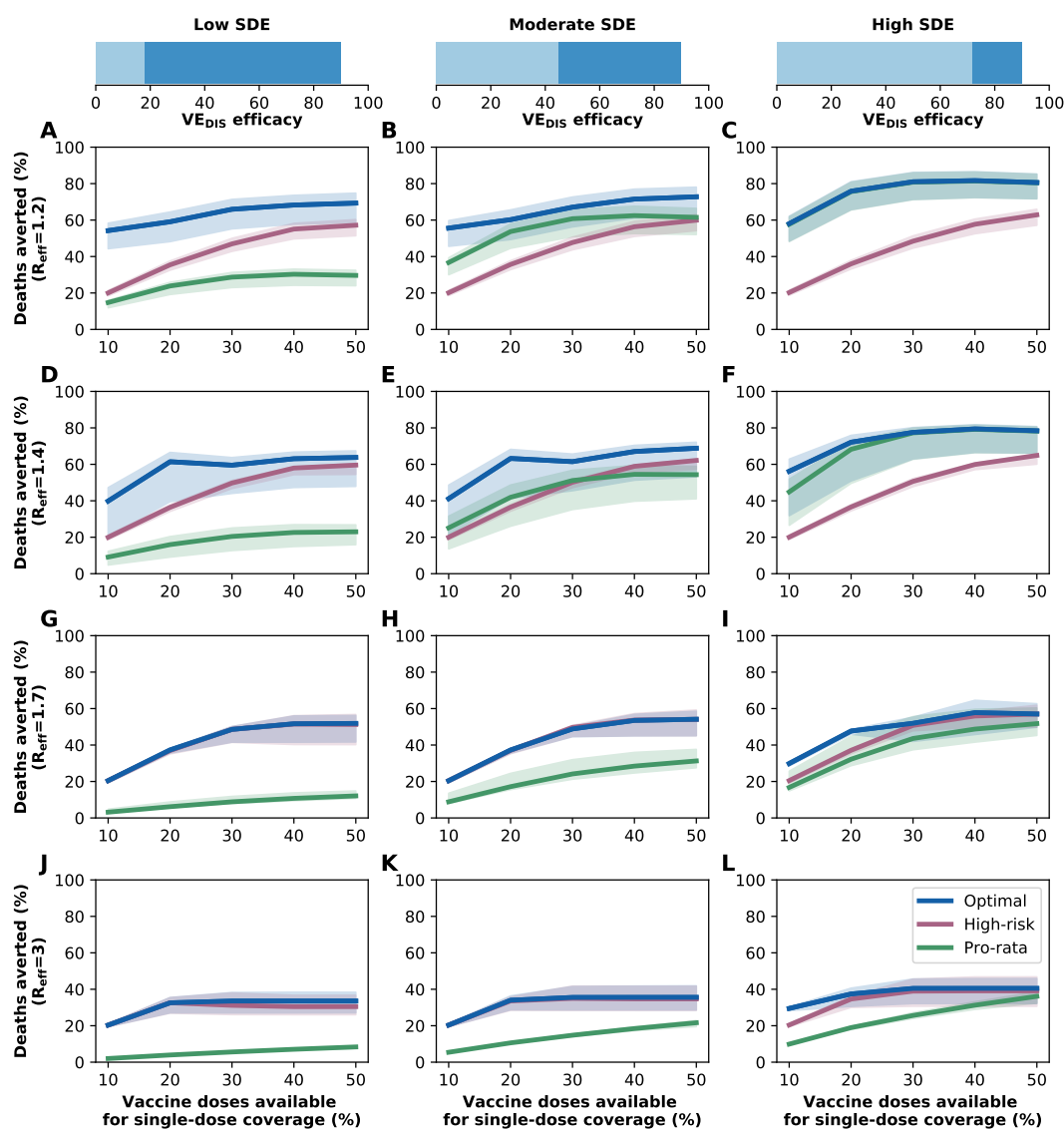


Figure 2: Percentage of deaths averted for different levels of SARS-CoV-2 transmission. Percentage of deaths averted for the optimal allocation strategies (blue), the *high-risk strategy* (pink) and the *pro-rata strategy* (green) with enough vaccine to cover 10-50% of the population with one dose. Each row represents a different level of SARS-CoV-2 transmission resulting in $R_{\text{eff}} = 1.2$ (A-C), 1.4 (D-F), 1.7 (G-I) or 3 (J-L). The columns correspond to assumptions that the single-dose efficacy (SDE) is low (left column, $VE_{\text{DIS}_1} = 18\%$), moderate (center column, $VE_{\text{DIS}_1} = 45\%$) or high (right column, $VE_{\text{DIS}_1} = 72\%$), corresponding 20, 50 or 80% of the 90% efficacy that is assumed following two doses of vaccine, respectively. Shaded areas represent results of 1,000 parameter simulations with the top and bottom 2.5% removed.

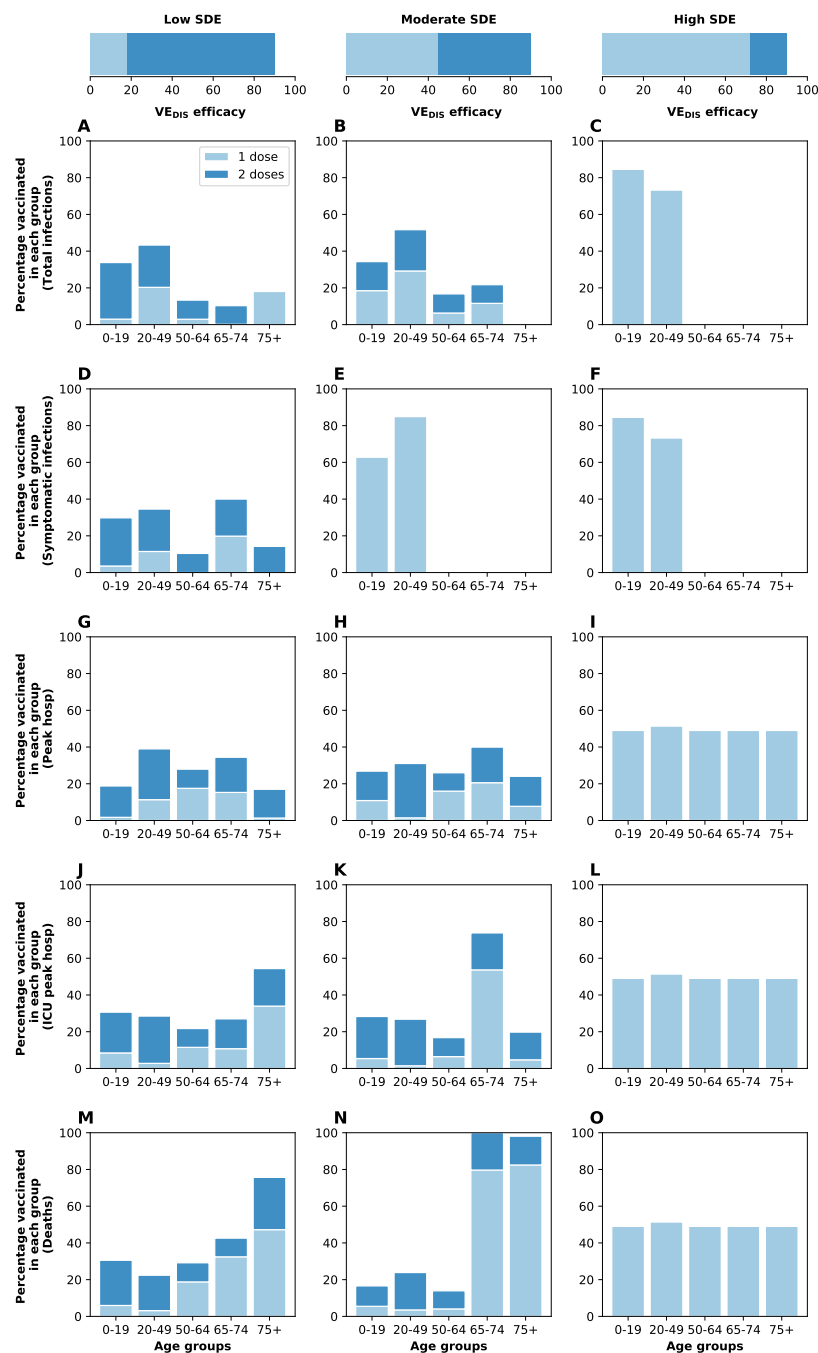


Figure 3: **Optimal vaccine allocation strategies for different disease metrics with 50% coverage.** Optimal vaccine allocation for a vaccine with $VE_{DIS} = 90\%$ and assuming enough vaccine to cover 50% of the population with a single dose (25% with two doses). Each row represents a different disease metric minimized: cumulative infections (A-C), cumulative symptomatic infections (D-F), non-ICU peak hospitalizations (G-I), ICU hospitalizations (J-L) and total deaths (M-O). The columns correspond to assumptions that the single-dose efficacy (SDE) is low (left column, $VE_{DIS1} = 18\%$), moderate (center column, $VE_{DIS1} = 45\%$) or high (right column, $VE_{DIS1} = 72\%$), corresponding 20, 50 or 80% of the 90% efficacy that is assumed following two doses of vaccine, respectively.

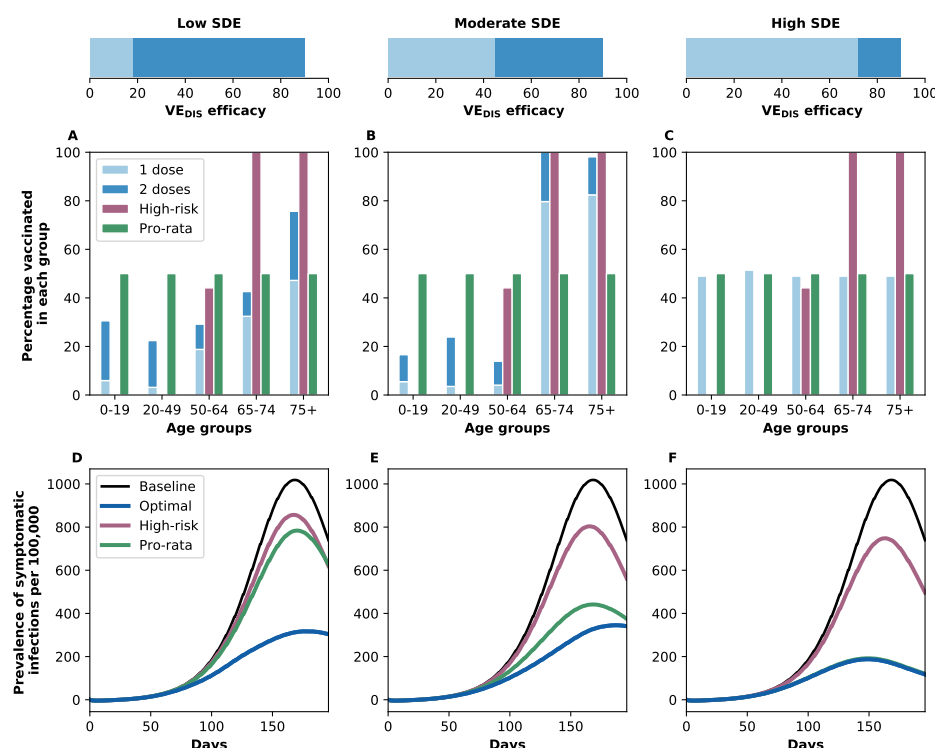


Figure 4: **A-C: Optimal pro-rata and high-risk allocation strategies with 50% coverage.** *Optimal* (light and dark blue), *high-risk* (pink) and *pro-rata* (green) allocation strategies assuming enough vaccine to cover 50% of the population with a single dose (25% with two doses). Within each panel, the bars represent the percentage vaccinated in each vaccination group. **D-E: Prevalence of symptomatic infections.** Prevalence of symptomatic infections (per 100,000) in the absence of vaccine (black), with the optimal allocation strategy to minimize deaths (blue), the *high-risk strategy* (pink) or the *pro-rata strategy* (green) with enough vaccine to cover 50% of the population with a single dose (25% with two doses). The columns correspond to assumptions that the single-dose efficacy (SDE) is low (left column, $VE_{DIS1} = 18\%$), moderate (center column, $VE_{DIS1} = 45\%$) or high (right column, $VE_{DIS1} = 72\%$), corresponding 20, 50 or 80% of the 90% efficacy that is assumed following two doses of vaccine, respectively.

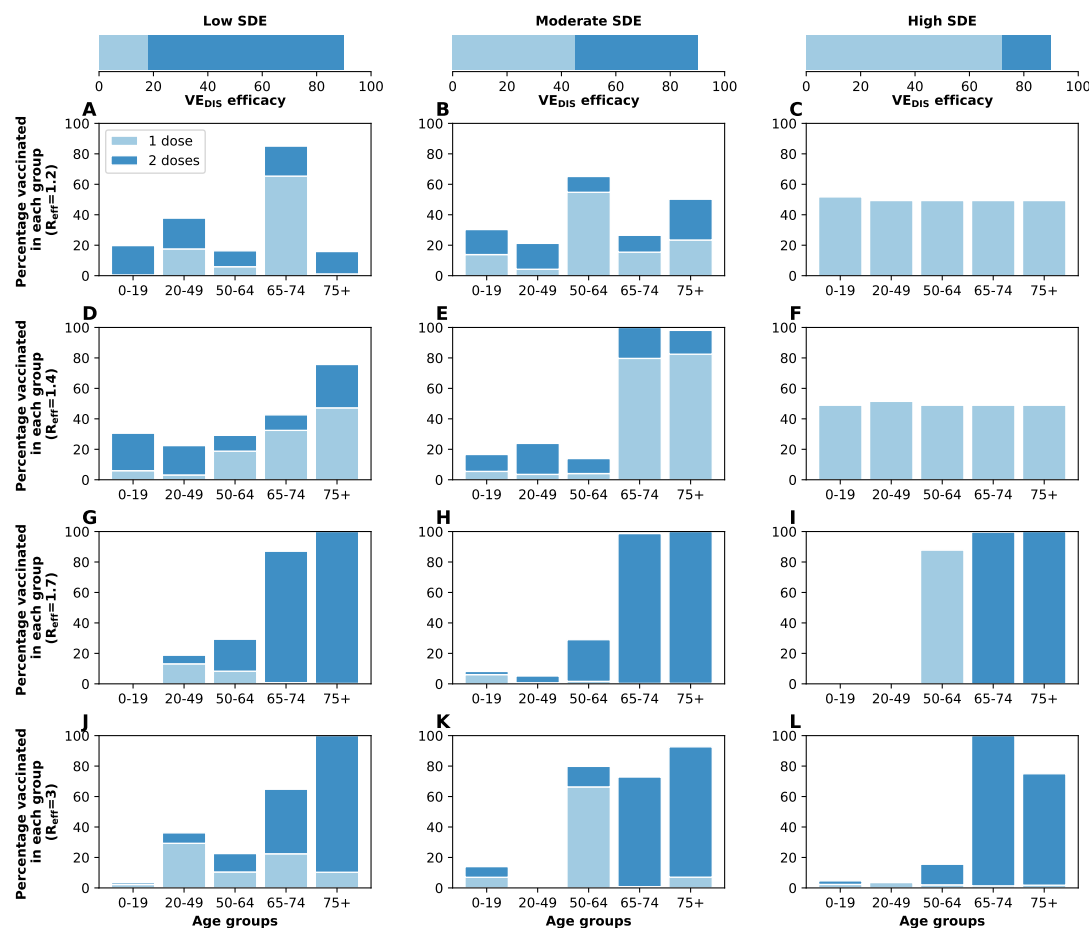


Figure 5: Optimal vaccine allocation for minimizing deaths for different levels of SARS-CoV-2 transmission and 50% coverage. Optimal vaccine allocation for minimizing deaths with a vaccine with $VE_{DIS} = 90\%$ and assuming enough vaccine to cover 50% of the population with one dose (or 25% with two doses). For each panel (A-L), the bars represent the total percentage of the population in each vaccination group to be vaccinated, split in those receiving one dose (light blue) and those receiving two doses (dark blue). Each row represents a different level of SARS-CoV-2 transmission resulting in an $R_{eff}=1.2$ (A-C), 1.4 (D-F), 1.7 (G-I) or 3 (J-L). The columns correspond to assumptions that the single-dose efficacy (SDE) is low (left column, $VE_{DIS1} = 18\%$), moderate (center column, $VE_{DIS1} = 45\%$) or high (right column, $VE_{DIS1} = 72\%$), corresponding 20, 50 or 80% of the 90% efficacy that is assumed following two doses of vaccine, respectively.

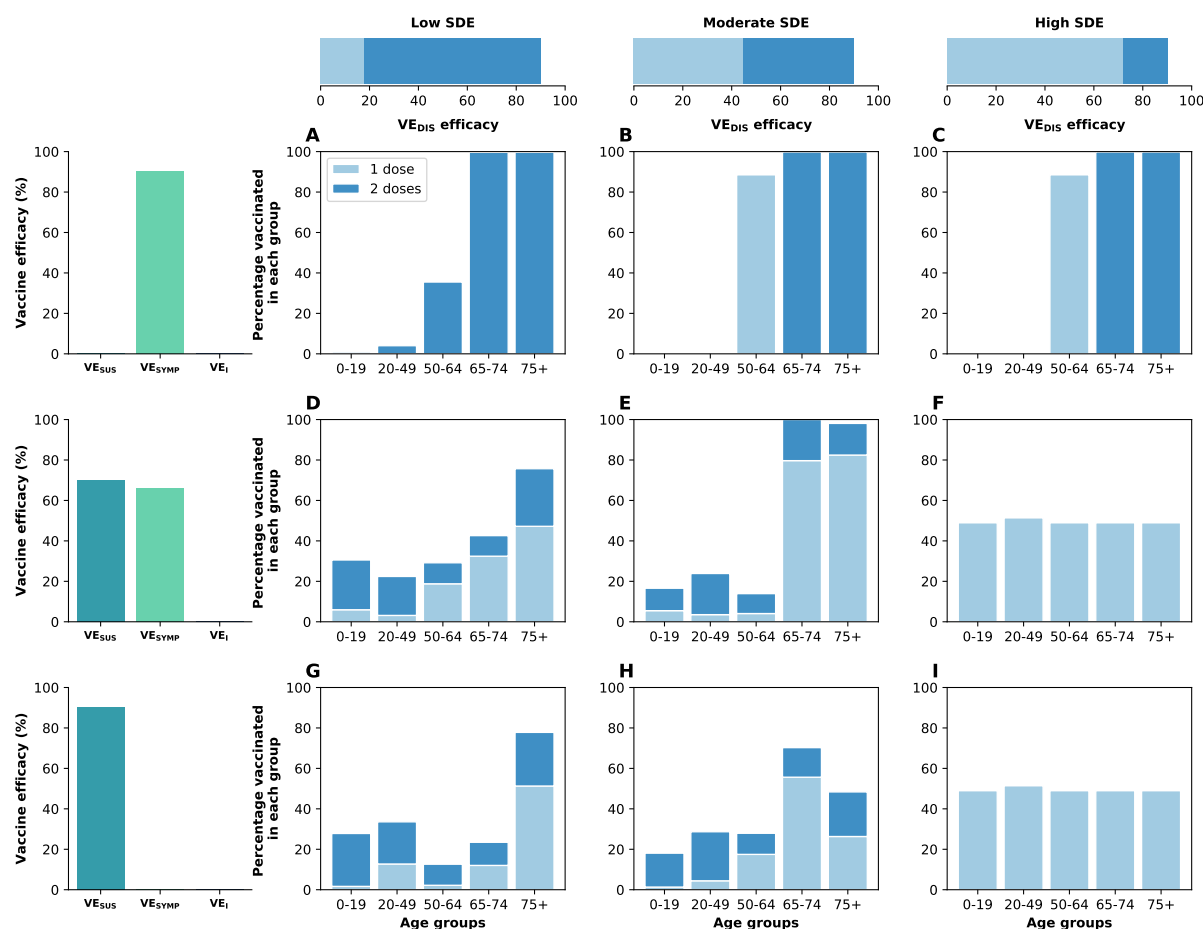


Figure 6: Optimal vaccine allocation to minimize deaths for different vaccine profiles with 50% coverage. Optimal vaccine allocation for minimizing deaths for a vaccine with $VE_{DIS} = 90\%$ and assuming enough vaccine to cover 50% of the population with a single dose (25% with two doses). For each panel (A-I), the bars represent the total percentage of the population in each vaccination group to be vaccinated, split in those receiving a single dose (light blue) and those receiving two doses (dark blue). Each row represents a different breakdown of $VE_{DIS} = 90\%$ as a function of VE_{SUS} and VE_{SYMP} . Top row (A-C): VE_{DIS} is mediated by a reduction in symptoms upon infection. Middle row (D-F): VE_{DIS} is mediated by a combination of reduction in susceptibility to infection and reduction of symptoms upon infection. Bottom row (G-I): VE_{DIS} is mediated by a reduction in susceptibility to infection. The columns correspond to assumptions that the single-dose efficacy (SDE) is low (left column, $VE_{DIS_1} = 18\%$), moderate (center column, $VE_{DIS_1} = 45\%$) or high (right column, $VE_{DIS_1} = 72\%$), corresponding 20, 50 or 80% of the 90% efficacy that is assumed following two doses of vaccine, respectively.

Figures

List of Supplementary Materials

Materials and Methods

Figs S1–S15

Tables S1–S3

References 51–69

Supplemental figures

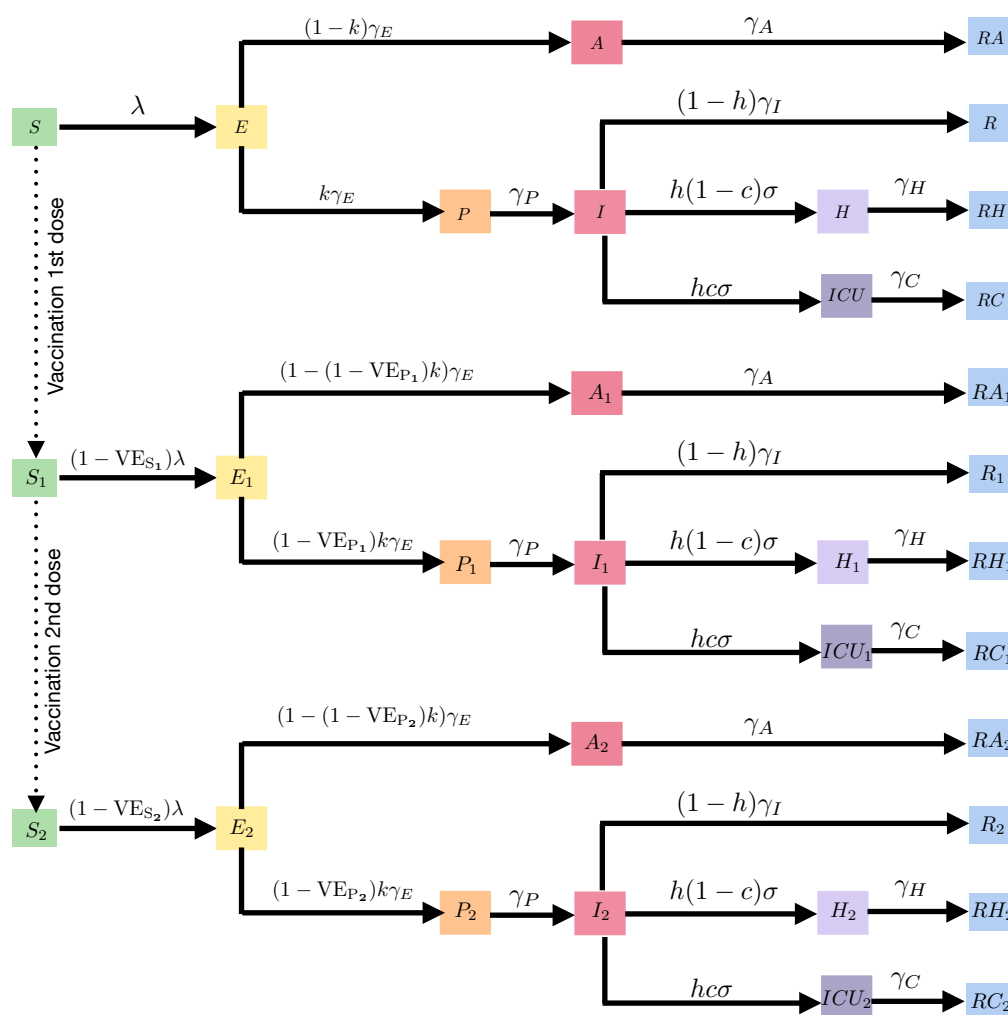


Figure S1: **Diagram of the SEIR model with vaccination with one or two doses of vaccine.** Age indices have been omitted for clarity.

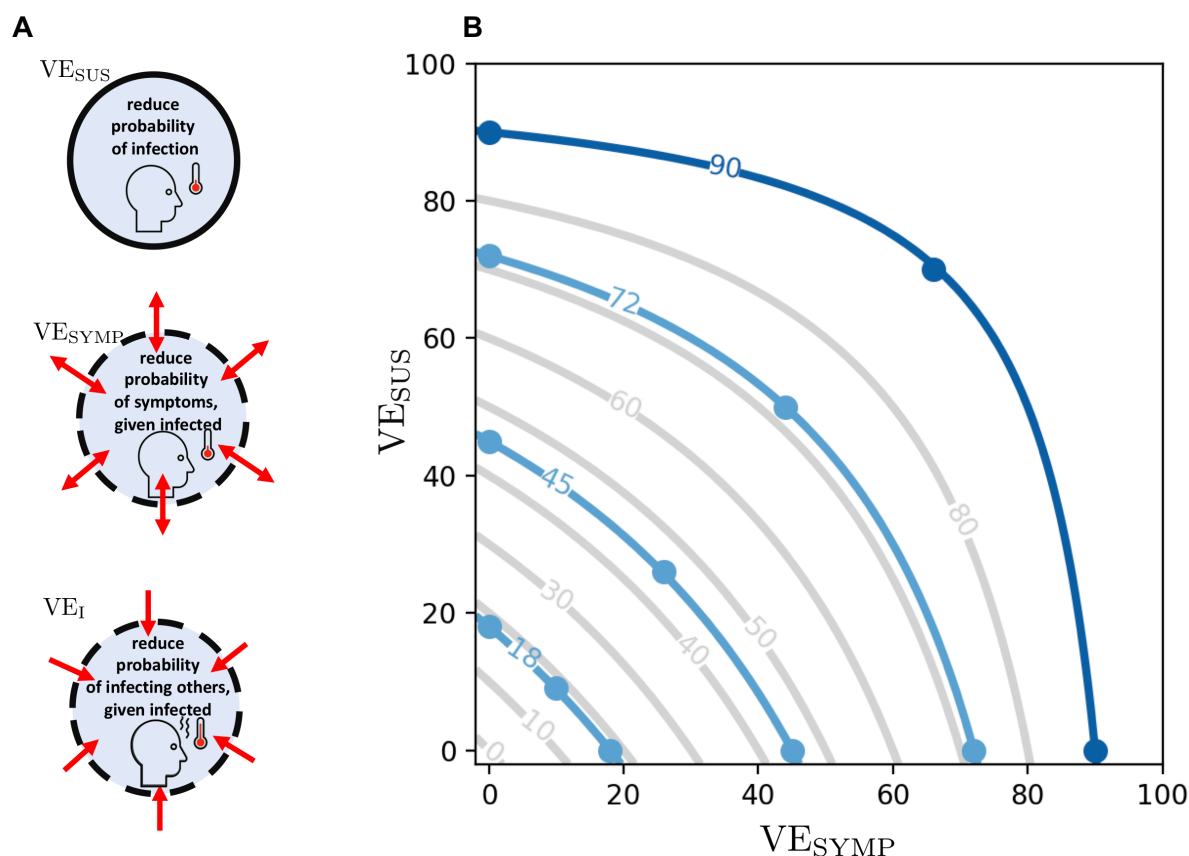


Figure S2: A: Different vaccine effects modeled. A vaccine can reduce the probability of infection, denoted by VE_{SUS} . In addition, it can reduce the probability of developing symptoms once infected, denoted VE_{SYMP} . Finally, it can reduce the infectiousness of a vaccinated person upon infection, denoted VE_I . We assumed that VE_{DIS} can be expressed as a combination of VE_{SUS} and VE_{SYMP} (see text). **B: Level curves for VE_{DIS} as a function of VE_{SUS} and VE_{SYMP} .** The light blue lines indicate the efficacies VE_{DIS_1} obtained after a first dose of vaccine considered in the main analysis. The dark blue line indicates the vaccine efficacy obtained after the full dosage (two doses) $VE_{DIS} = 90\%$.

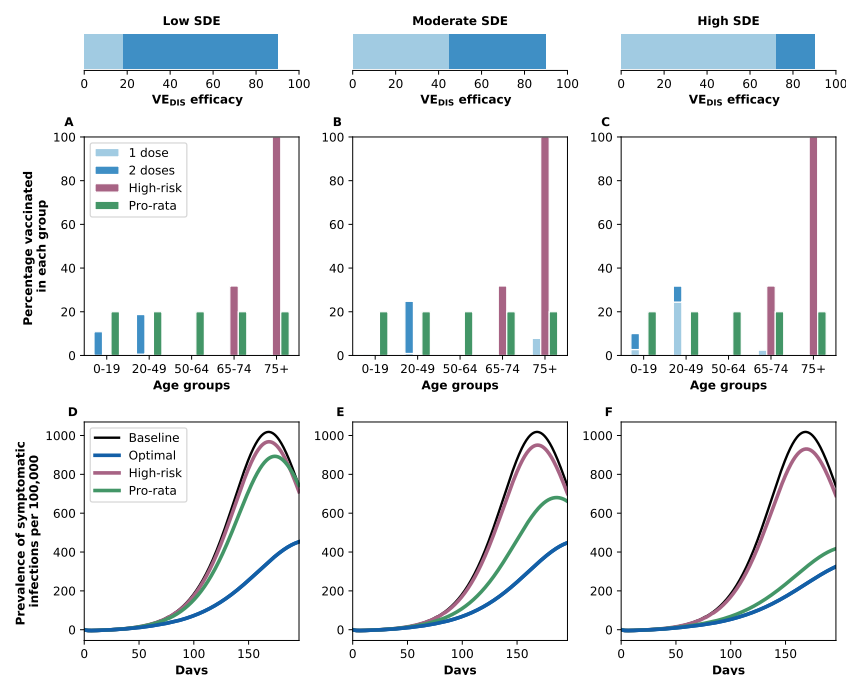


Figure S3: **A–C: Optimal, pro-rata and high-risk strategies to minimize deaths with enough vaccine to cover 20% of the population with a single dose (10% with two doses).** *Optimal* (light and dark blue), *high-risk* (pink) and *pro-rata* (green) allocation strategies. Within each panel, the bars represent the percentage vaccinated in each vaccination group. **D–F: Prevalence of symptomatic infections.** Prevalence of symptomatic (per 100,000) in absence of vaccine (black), with the optimal allocation strategy to minimize deaths (blue), the *high-risk* strategy (pink) or the *pro-rata* strategy (green).

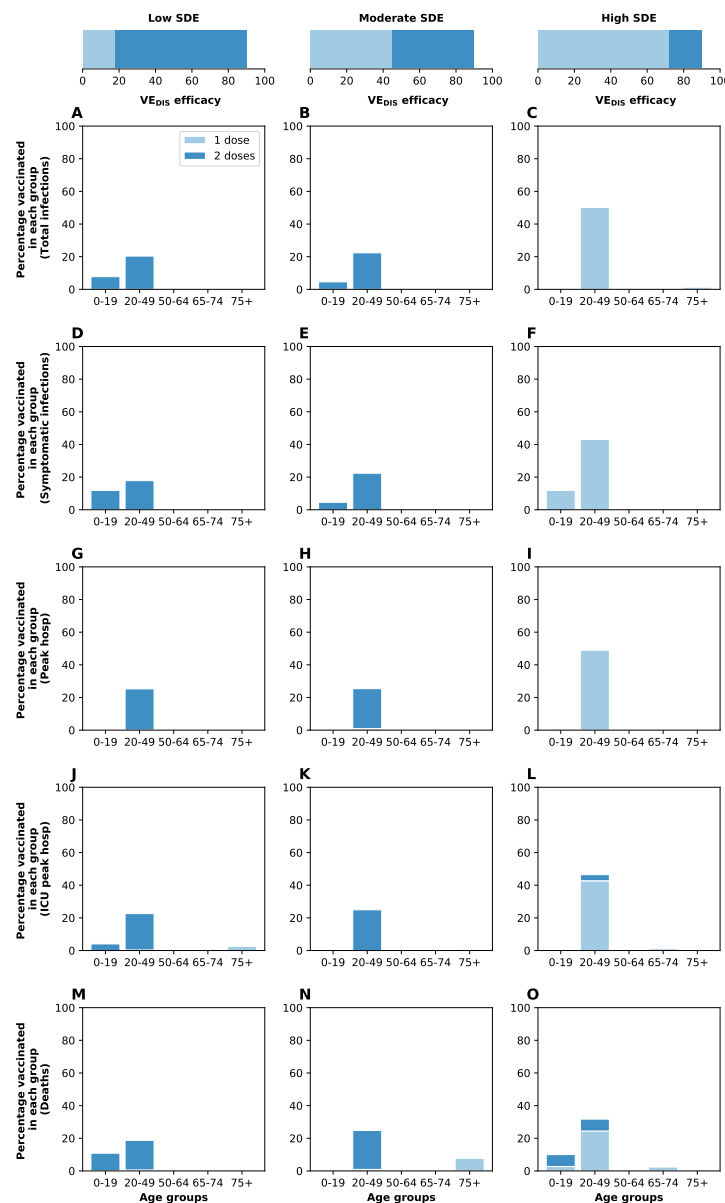


Figure S4: Optimal allocation strategies for different disease metrics with enough vaccine to cover 10 to 50% of the population with a single dose (5–10% with two doses). Optimal vaccine allocation for a vaccine with $VE_{DIS} = 90\%$ and assuming enough vaccine to cover 50% of the population with a single dose (25% with two doses). Each row represents an objective function minimized: cumulative infections (A–C), cumulative symptomatic infections (D–F), non-ICU peak hospitalizations (G–I), ICU hospitalizations (J–L) and total deaths (M–O). The columns correspond to assumptions that the single-dose efficacy (SDE) is low (left column, $VE_{DIS1} = 18\%$), moderate (center column, $VE_{DIS1} = 45\%$) or high (right column, $VE_{DIS1} = 72\%$), corresponding 20, 50 or 80% of the 90% efficacy that is assumed following two doses of vaccine, respectively.

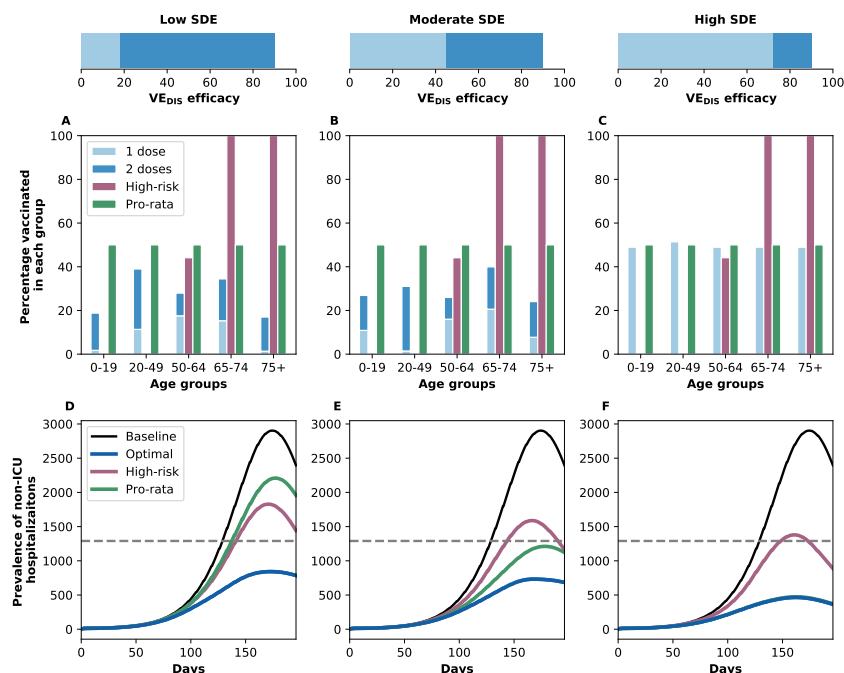


Figure S5: **A–C: Optimal, pro-rata and high-risk strategies to minimize non-ICU hospitalizations with enough vaccine to cover 50% of the population with a single dose (25% with two doses).** *Optimal* (light and dark blue), *high-risk* (pink) and *pro-rata* (green) allocation strategies to minimize peak non-ICU hospitalizations. Within each panel, the bars represent the percentage vaccinated in each vaccination group. **D–F: Prevalence of non-ICU hospitalizations.** Prevalence of non-ICU hospitalizations in absence of vaccine (black), with the optimal allocation strategy to minimize non-ICU hospitalizations (blue), the *high-risk strategy* (pink) or the *pro-rata strategy* (green). The gray dashed line indicates 10% occupancy of non-ICU beds in WA state. The columns correspond to assumptions that the single-dose efficacy (SDE) is low (left column, $VE_{DIS1} = 18\%$), moderate (center column, $VE_{DIS1} = 45\%$) or high (right column, $VE_{DIS1} = 72\%$), corresponding 20, 50 or 80% of the 90% efficacy that is assumed following two doses of vaccine, respectively.

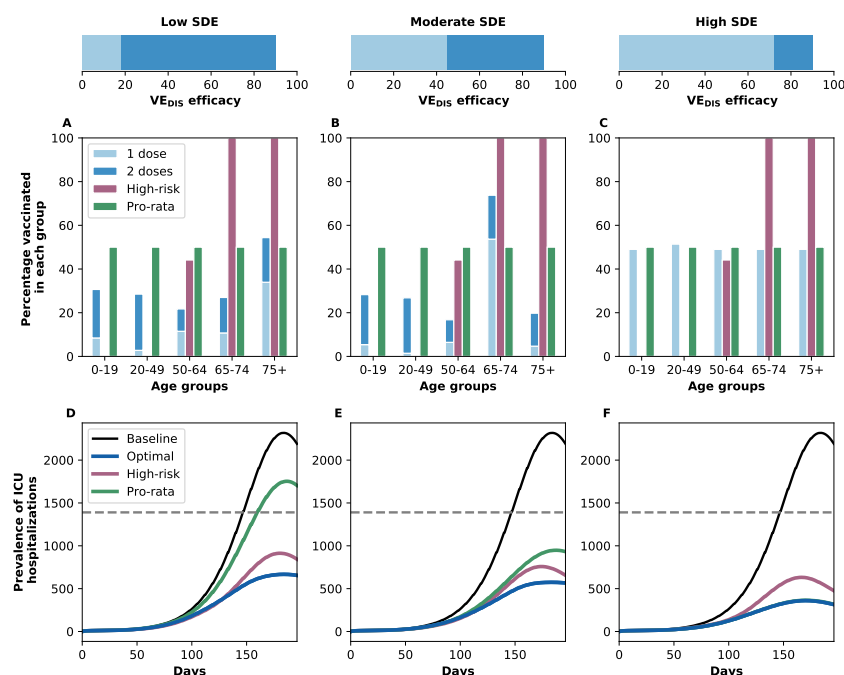


Figure S6: **A–C: Optimal, pro-rata and high-risk strategies to minimize ICU hospitalizations with enough vaccine to cover 50% of the population with a single dose (25% with two doses).** *Optimal* (light and dark blue), *high-risk* (pink) and *pro-rata* (green) allocation strategies to minimize peak ICU hospitalizations. Within each panel, the bars represent the percentage vaccinated in each vaccination group. **D–F: Prevalence of ICU hospitalizations.** Prevalence of ICU hospitalizations in absence of vaccine (black), with the optimal allocation strategy to minimize deaths (blue), the *high-risk strategy* (pink) or the *pro-rata strategy* (green). The gray dashed line indicates the number of ICU beds in WA state. The columns correspond to assumptions that the single-dose efficacy (SDE) is low (left column, $VE_{DIS1} = 18\%$), moderate (center column, $VE_{DIS1} = 45\%$) or high (right column, $VE_{DIS1} = 72\%$), corresponding 20, 50 or 80% of the 90% efficacy that is assumed following two doses of vaccine, respectively.

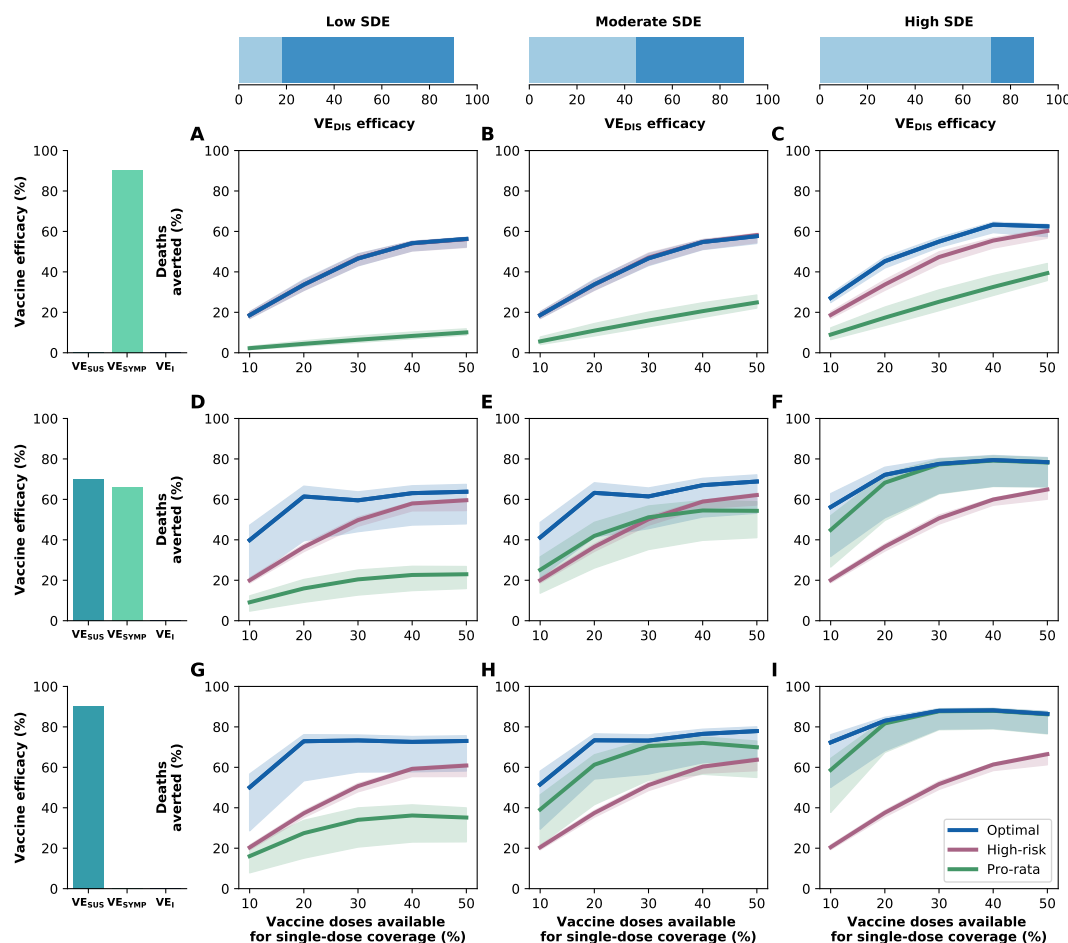


Figure S7: Percentage of deaths averted for different vaccine profiles. Percentage of deaths averted for the optimal allocation strategies (blue), the *high-risk strategy* (pink) and the *pro-rata strategy* (green) with enough vaccine to cover 10–50% of the population with one dose. Each row represents a different breakdown of $VE_{DIS} = 90\%$ as a function of VE_{SUS} and VE_{SYMP} . Top row (A–C): VE_{DIS} is mediated by a reduction in symptoms upon infection. Middle row (D–F): VE_{DIS} is mediated by a combination of reduction in susceptibility to infection and reduction of symptoms upon infection. Bottom row (G–I): VE_{DIS} is mediated by a reduction in susceptibility to infection. The columns correspond to assumptions that the single-dose efficacy (SDE) is low (left column, $VE_{DIS1} = 18\%$), moderate (center column, $VE_{DIS1} = 45\%$) or high (right column, $VE_{DIS1} = 72\%$), corresponding 20, 50 or 80% of the 90% efficacy that is assumed following two doses of vaccine, respectively. Shaded areas represent results of 1,000 parameter simulations with the top and bottom 2.5% removed.

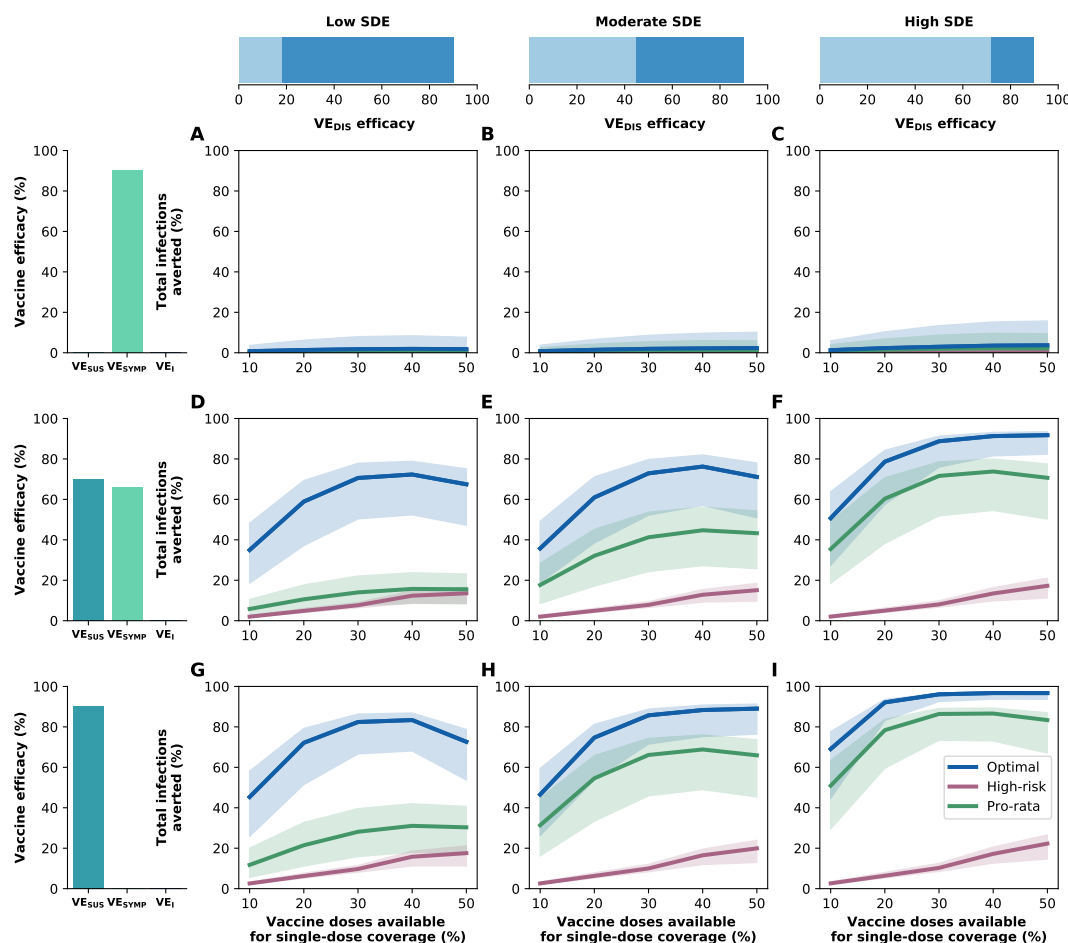
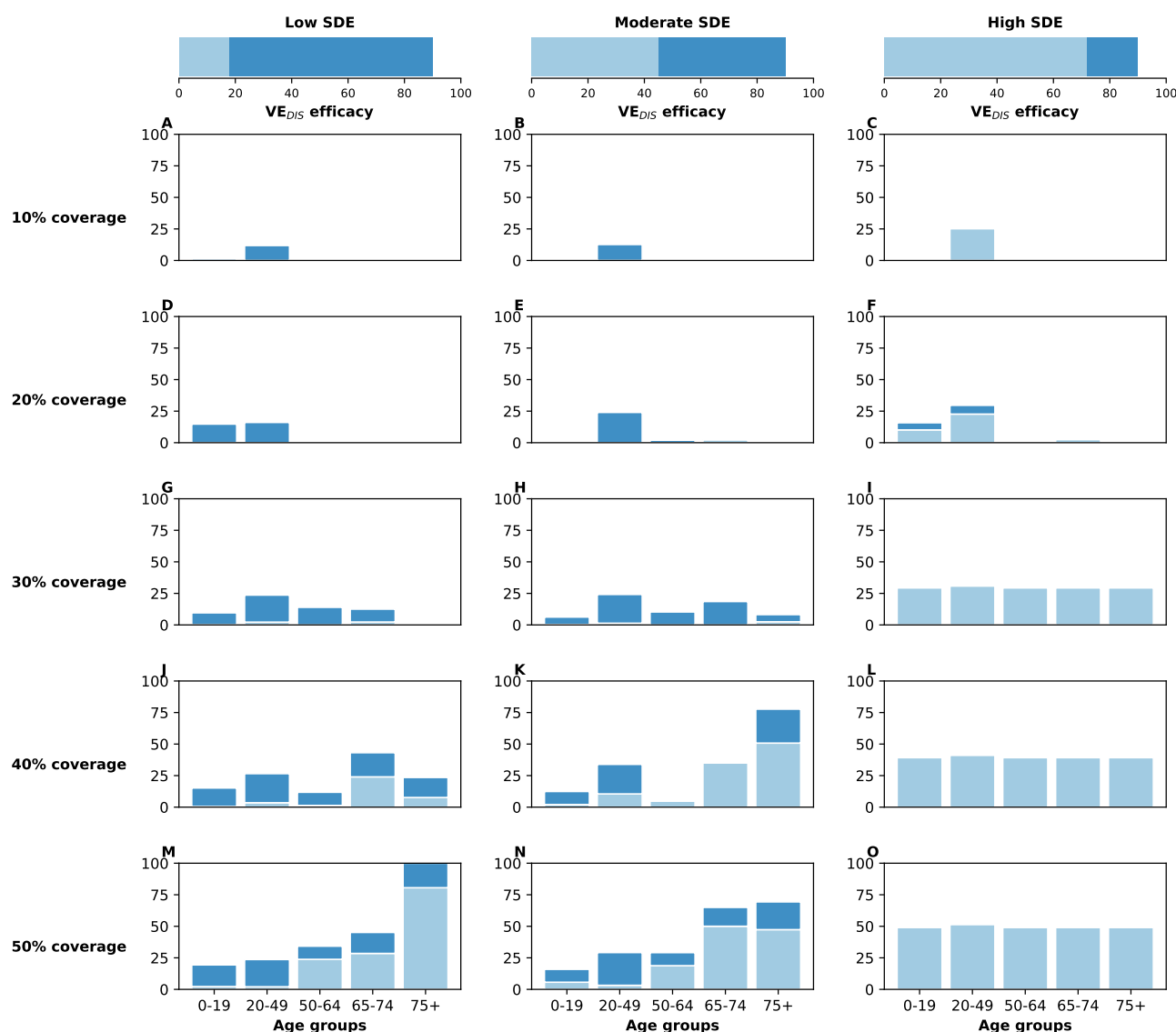


Figure S8: Percentage of cumulative infections averted for different vaccine profiles. Percentage of cumulative infections averted for the optimal allocation strategies (blue), the *high-risk* strategy (pink) and the *pro-rata* strategy (green) with enough vaccine to cover 10–50% of the population with one dose. Each row represents a different breakdown of $VE_{DIS} = 90\%$ as a function of VE_{SUS} and VE_{SYMP} . Top row (A–C): VE_{DIS} is mediated by a reduction in symptoms upon infection. Middle row (D–F): VE_{DIS} is mediated by a combination of reduction in susceptibility to infection and reduction of symptoms upon infection. Bottom row (G–I): VE_{DIS} is mediated by a reduction in susceptibility to infection. The columns correspond to assumptions that the single-dose efficacy (SDE) is low (left column, $VE_{DIS,1} = 18\%$), moderate (center column, $VE_{DIS,1} = 45\%$) or high (right column, $VE_{DIS,1} = 72\%$), corresponding 20, 50 or 80% of the 90% efficacy that is assumed following two doses of vaccine, respectively. Shaded areas represent results of 1,000 parameter simulations with the top and bottom 2.5% removed.



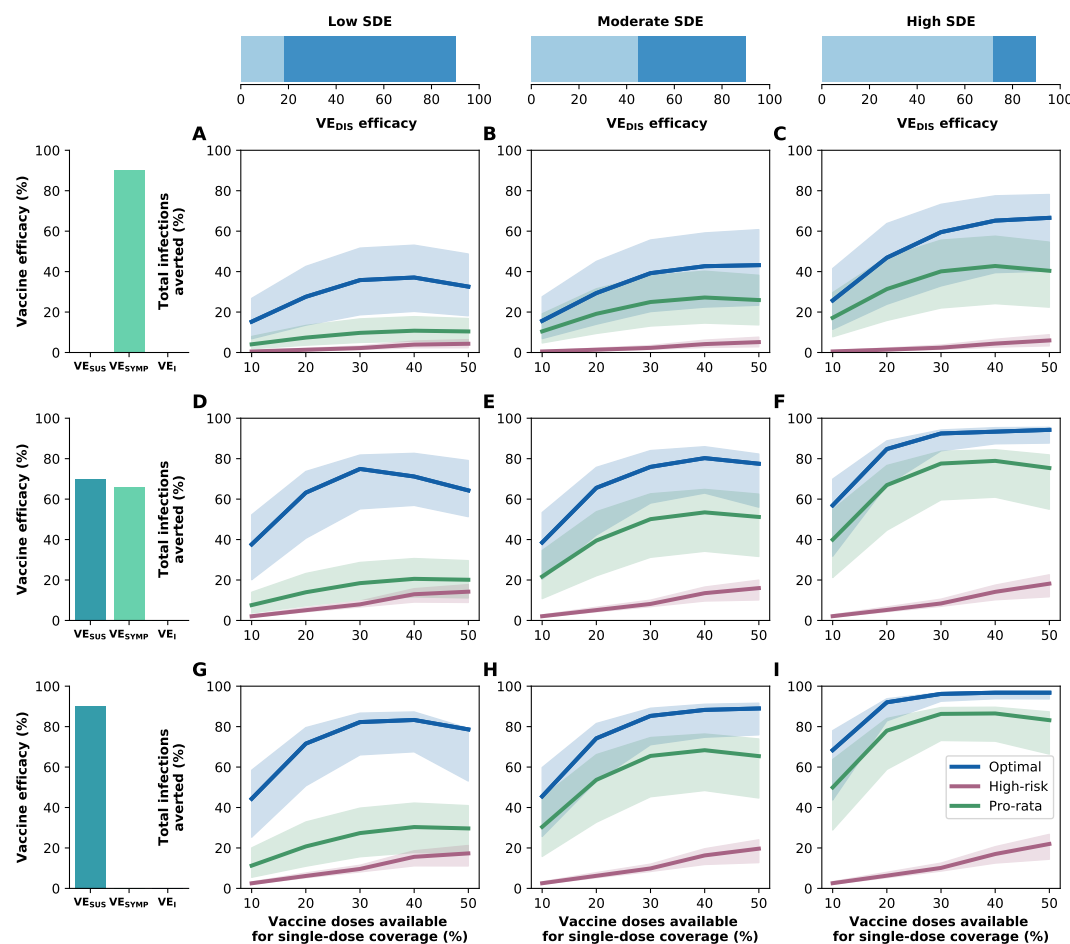
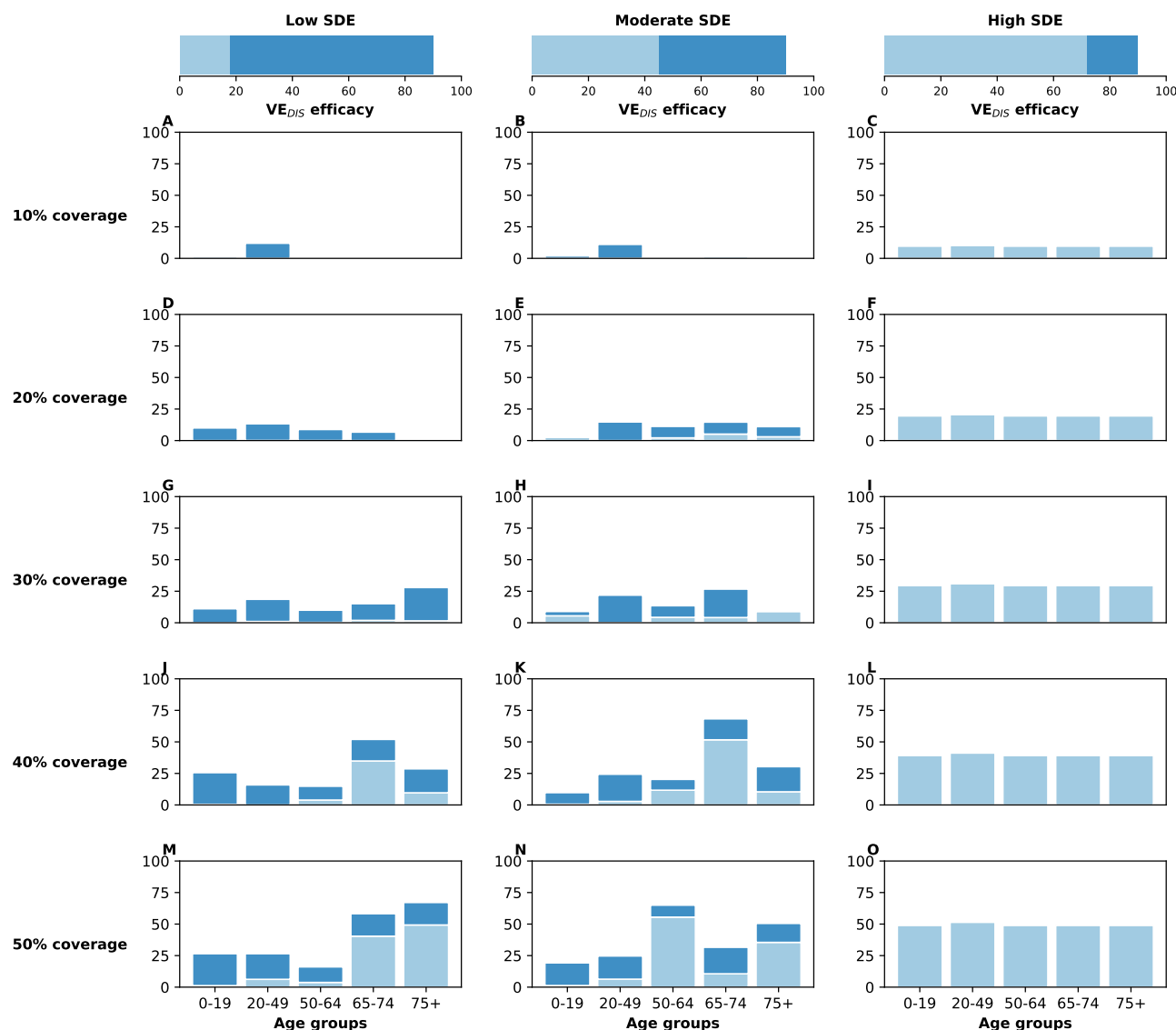


Figure S10: Percentage of cumulative infections averted for different vaccine profiles assuming asymptomatic infections are 50% less infectious than symptomatic ones. Percentage of cumulative infections averted for the optimal allocation strategies (blue), the *high-risk strategy* (pink) and the *pro-rata strategy* (green) with enough vaccine to cover 10–50% of the population with one dose. Each row represents a different breakdown of $VE_{DIS} = 90\%$ as a function of VE_{SUS} and VE_{SYMP} . Top row (A–C): VE_{DIS} is mediated by a reduction in symptoms upon infection. Middle row (D–F): VE_{DIS} is mediated by a combination of reduction in susceptibility to infection and reduction of symptoms upon infection. Bottom row (G–I): VE_{DIS} is mediated by a reduction in susceptibility to infection. The columns correspond to assumptions that the single-dose efficacy (SDE) is low (left column, $VE_{DIS1} = 18\%$), moderate (center column, $VE_{DIS1} = 45\%$) or high (right column, $VE_{DIS1} = 72\%$), corresponding to 20, 50 or 80% of the 90% efficacy that is assumed following two doses of vaccine, respectively. Shaded areas represent results of 1,000 parameter simulations with the top and bottom 2.5% removed.



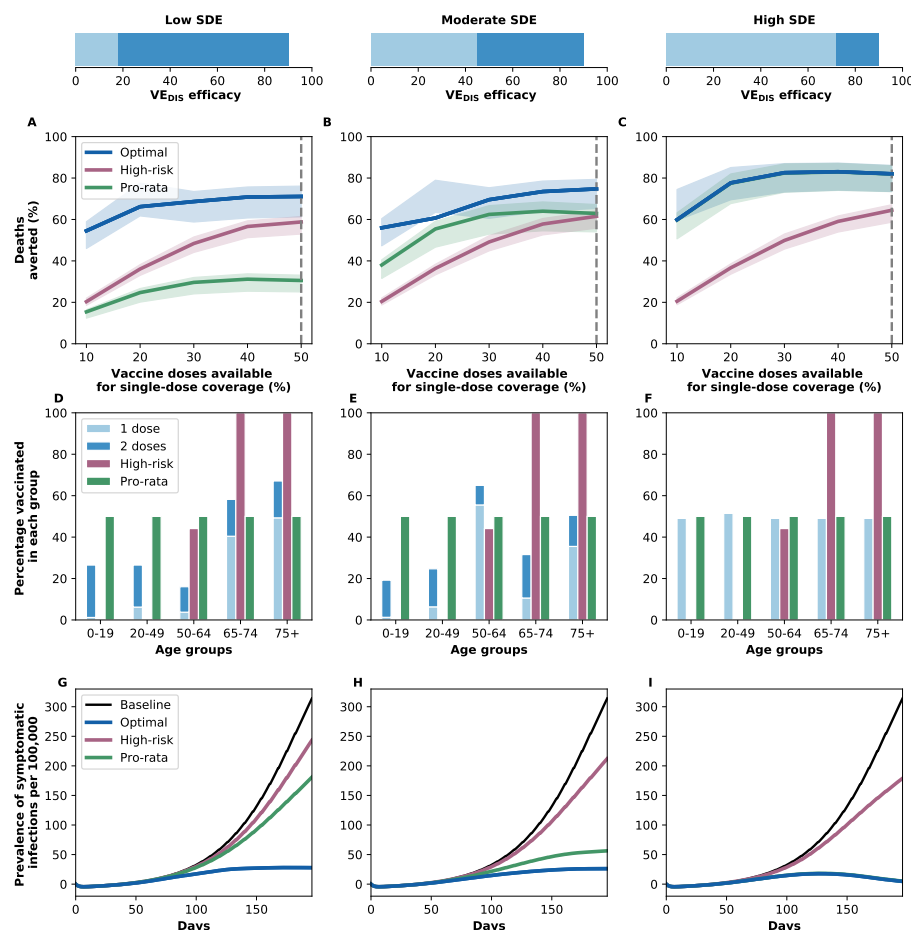


Figure S12: A–C. Percentage of deaths averted: Percentage of deaths averted for the optimal allocation strategies (blue), the *high-risk strategy* (pink) and the *pro-rata strategy* (green) with enough vaccine to cover 10–50% of the population with a single dose (5–25% with two doses). **D–F. Allocation strategies:** *Optimal* (light and dark blue), *high-risk* (pink) and *pro-rata* (green) allocation strategies with enough vaccine to cover 50% of the population with one dose (25% with two doses). Within each panel, the bars represent the percentage vaccinated in each vaccination group. **G–I. Prevalence of symptomatic infections:** Prevalence of symptomatic infections (per 100,000) in absence of vaccine (black), with the optimal allocation strategy to minimize deaths (blue), the *high-risk strategy* (pink) or the *pro-rata strategy* (green) with enough vaccine to cover 50% of the population with one dose (25% with two doses). The columns correspond to assumptions that the single-dose efficacy (SDE) is low (left column, $VE_{DIS_1} = 18\%$), moderate (center column, $VE_{DIS_1} = 45\%$) or high (right column, $VE_{DIS_1} = 72\%$), corresponding 20, 50 or 80% of the 90% efficacy that is assumed following two doses of vaccine, respectively. Here, we assumed 20% of the population has been infected and is immune at the beginning of the simulations.

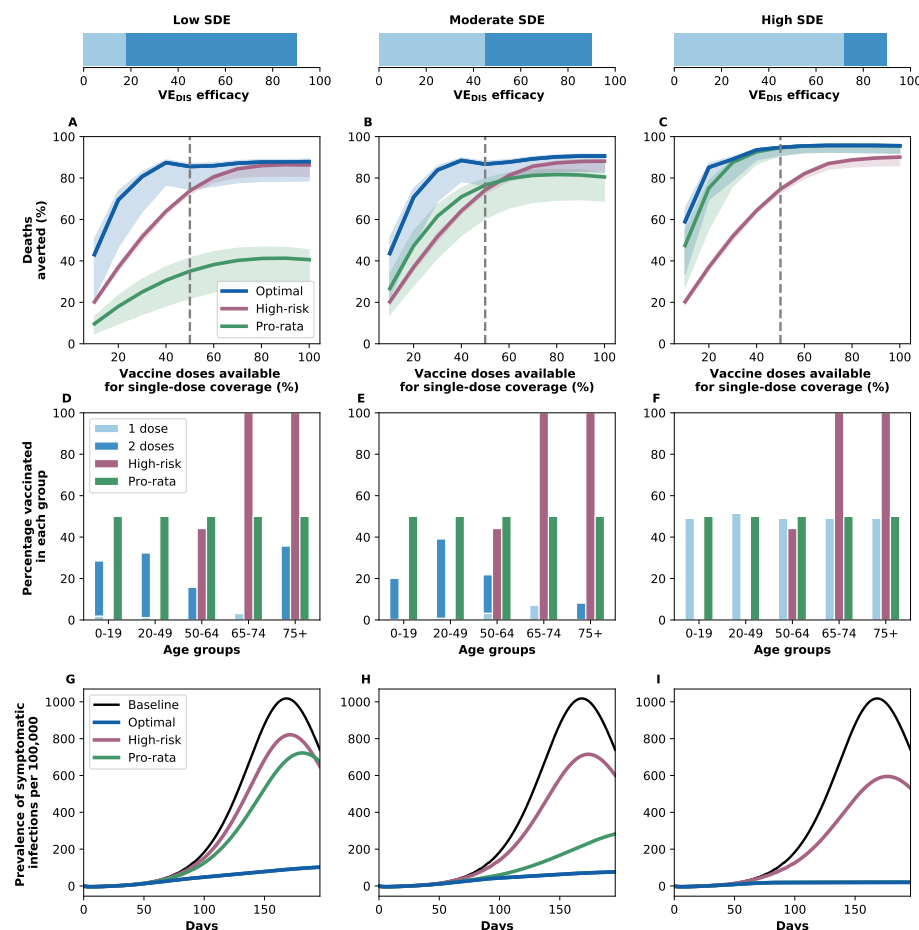
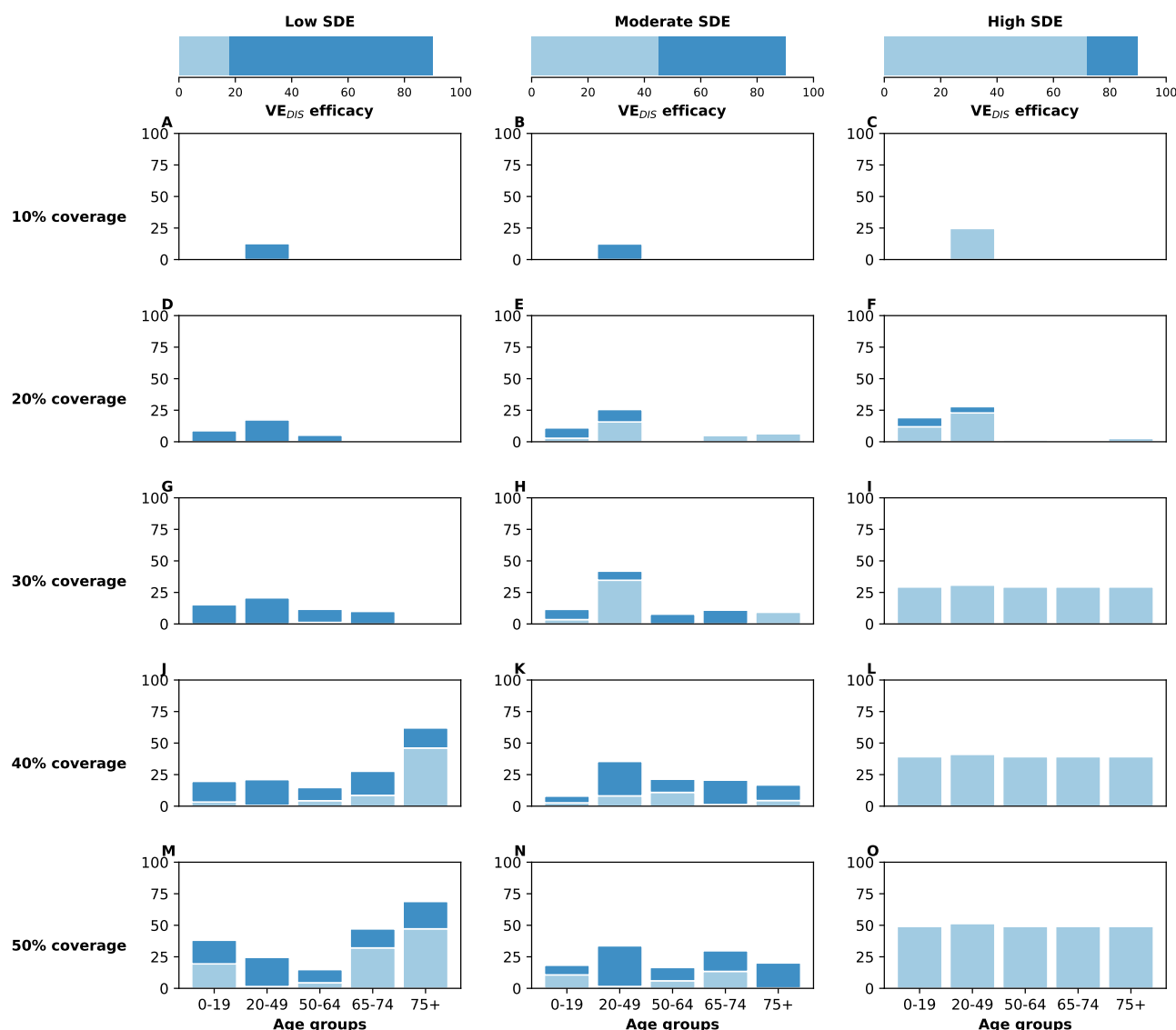


Figure S13: A–C. Percentage of deaths averted: Percentage of deaths averted for the optimal allocation strategies (blue), the *high-risk strategy* (pink) and the *pro-rata strategy* (green) with enough vaccine to cover 10–100% of the population with one dose (5–50% with two doses), administering 300K doses per week. Shaded areas represent results of 1,000 parameter simulations with the top and bottom 2.5% removed. **D–F. Allocation strategies:** *Optimal* (light and dark blue), *high-risk* (pink) and *pro-rata* (green) allocation strategies with enough vaccine to cover 50% of the population with a single dose (25% with two doses). Within each panel, the bars represent the percentage vaccinated in each vaccination group. **G–I. Prevalence of symptomatic infections:** Prevalence of symptomatic infections (per 100,000) in absence of vaccine (black), with the optimal allocation strategy to minimize deaths (blue), the *high-risk strategy* (pink) or the *pro-rata strategy* (green) with enough vaccine to cover 20% of the population with one dose (10% with two doses). The columns correspond to assumptions that the single-dose efficacy (SDE) is low (left column, $VE_{DIS_1} = 18\%$), moderate (center column, $VE_{DIS_1} = 45\%$) or high (right column, $VE_{DIS_1} = 72\%$), corresponding 20, 50 or 80% of the 90% efficacy that is assumed following two doses of vaccine, respectively. Here, we assumed 300K doses of vaccine delivered per week. At this rate, 100% of the population can be vaccinated with a single dose in our time horizon.



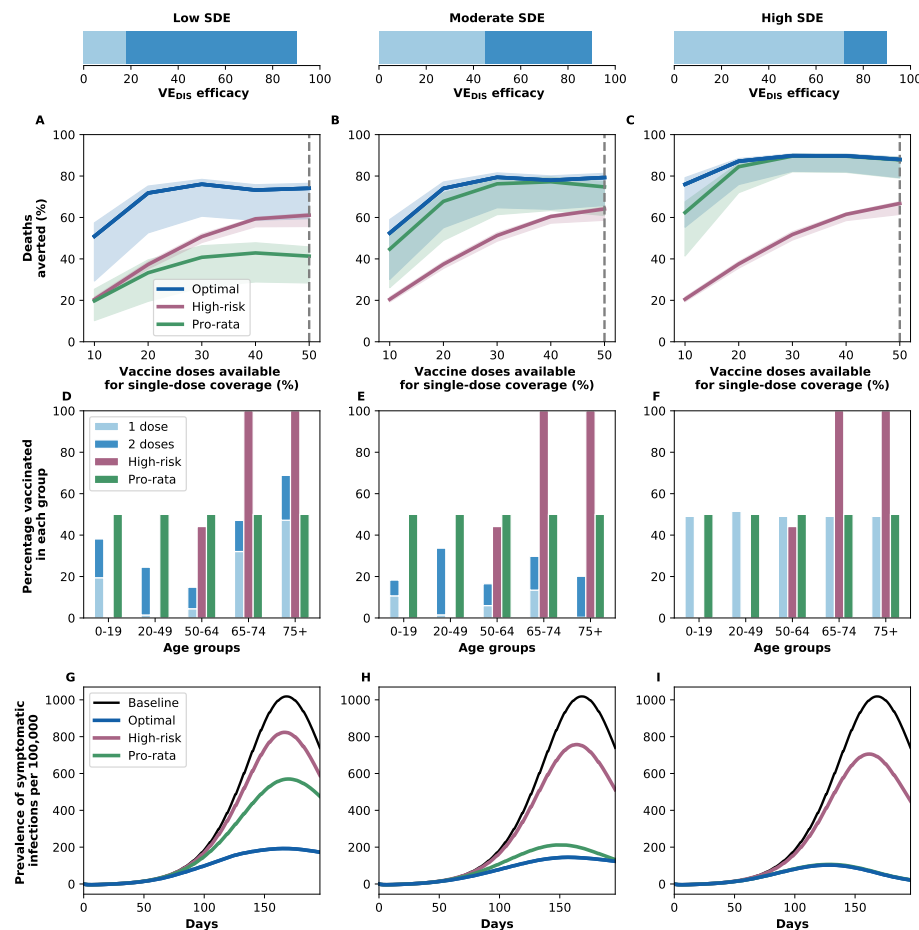


Figure S15: A–C. Percentage of deaths averted assuming that $VE_I = 70\%$: Percentage of deaths averted for the optimal allocation strategies (blue), the *high-risk strategy* (pink) and the *pro-rata strategy* (green) with enough vaccine to cover 10–50% of the population with one dose (5–25% with two doses). Shaded areas represent results of 1,000 parameter simulations with the top and bottom 2.5% removed. **D–F. Allocation strategies:** *Optimal* (light and dark blue), *high-risk* (pink) and *pro-rata* (green) allocation strategies with enough vaccine to cover 50% of the population with a single dose (25% with two doses). Within each panel, the bars represent the percentage vaccinated in each vaccination group. **G–I. Prevalence of symptomatic infections:** Prevalence of symptomatic infections (per 100,000) in absence of vaccine (black), with the optimal allocation strategy to minimize deaths (blue), the *high-risk strategy* (pink) or the *pro-rata strategy* (green) with enough vaccine to cover 20% of the population with one dose (10% with two doses). The columns correspond to assumptions that the single-dose efficacy (SDE) is low (left column, $VE_{DIS1} = 18\%$), moderate (center column, $VE_{DIS1} = 45\%$) or high (right column, $VE_{DIS1} = 72\%$), corresponding 20, 50 or 80% of the 90% efficacy that is assumed following two doses of vaccine, respectively. Here, we assumed that $VE_I = 70\%$.

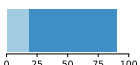
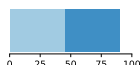
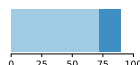
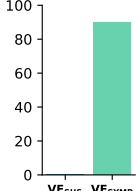
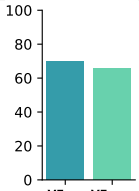
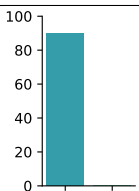
							TOTAL	
	$VE_{DIS_1} = 18\%$		$VE_{DIS_1} = 45\%$		$VE_{DIS_1} = 72\%$		$VE_{DIS} = 90\%$	
	VE_{SUS_1}	VE_{SYMP_1}	VE_{SUS_1}	VE_{SYMP_1}	VE_{SUS_1}	VE_{SYMP_1}	VE_{SUS}	VE_{SYMP}
 Vaccine mediated mainly by reducing symptoms upon infection	0%	18%	0%	45%	0%	72%	0%	90%
 Vaccine mediated by reducing symptoms upon infection and reducing susceptibility to infection	9%	10%	26%	26%	50%	44%	70%	66%
 Vaccine mediated mainly by reducing susceptibility to infection	18%	0%	45%	0%	72%	0%	90%	0%

Table S1: Description of vaccine efficacies used in the model.

Supplemental Tables

Parameter	Meaning	Value (Range)	Reference
$1/\sigma$	mean duration of latent period	3 (1.5–4.5) d	[53, 54]
$1/\gamma_P$	mean pre-symptomatic period	2 (1–3) d	[55]
$1/\gamma_A$	mean infectious period of asymptomatic infections	5 (3–8) d	assumed ^a
$1/\gamma_S$	mean infectious period of symptomatic infections after developing symptoms	3 (2–5) d	[56, 57]
$1/\gamma_H$	mean duration of non-ICU hospitalization	age-stratified	[19]
$1/\gamma_C$	mean duration of ICU hospitalization	age-stratified	[19]
k	proportion of infections that are symptomatic	0.6 (0.4–0.8)	[19, 58, 59]
h	proportion of symptomatic infections requiring hospitalization	age-stratified	[42]
c	proportion of hospitalizations requiring ICU	age-stratified	[42]
d	proportion of hospitalized who died	age-stratified	[43]
r_A	relative infectiousness of asymptomatic infections ^b	1 (0.5)	[19]
r_H	relative infectiousness of hospitalized infections	0	assumed
r_P	relative infectiousness of pre-symptomatic infections ^c	1 (0.7–1.3)	
σ	mean time from symptom onset to hospitalization	3.8	[60]
R_0	basic reproductive number	3	[61, 62]
R_{eff}	effective reproductive number	1.2, 1.4, 1.7, 3	assumed ^d
β	transmission coefficient	calculated	—
\mathcal{M}	contact matrix	—	[18]
N	total population	7,615,000	[63]
$R(0)$	recovered proportion of the total population at $t = 0$	0.1 (0.2)	assumed

^aassumed to match the duration of infectiousness of symptomatic infections

^bwith respect to symptomatic not hospitalized infections

^cwith respect to symptomatic not hospitalized infections

^dsee table S3 for details.

Table S2: Description of parameters used in the model.

R_{eff}	Home	Work	Other locations	School
1.2	1	0.6	0.2	0.1
1.4	1	0.6	0.4	0.1
1.7	1	0.6	0.5	0.5
3	1	1	1	1

Table S3: Multipliers used based on the contact matrices given in Prem et al. [18].

Mathematical model

Transmission model:

We built upon our previous model of SARS-CoV-2 transmission and vaccination with 16 age groups: 0–4, 5–9, 10–14, 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–74, and 75+ [17]. We used the population of Washington state (7.6 million people, [63]) and US demographics [64]. For each age group i , our model tracks susceptible S_i , exposed E_i , asymptomatic A_i , pre-symptomatic P_i and symptomatic infected individuals classed by disease severity (assumed to be equally infectious). Symptomatic individuals have one of three fates: they become mildly symptomatic I_i , hospitalized in a non-ICU ward H_i , or hospitalized requiring intensive care, ICU_i . After infection, individuals move to the respective recovered classes: recovered asymptomatic, mildly symptomatic, non-ICU hospitalized and ICU hospitalized (denoted by RA_i , R_i , RH_i and RC_i respectively). We assumed that asymptomatic and symptomatic infections are equally infectious (alternative scenario: Sensitivity Analysis, SI) and confer equal immunity. Further, we assumed that both naturally-induced and vaccine-induced immunity are long lasting, so that there is no waning during the time period analyzed. In addition, we modeled vaccinated individuals with one or two doses of vaccine, (with analogous compartments indexed by $j = 1$ or 2 respectively), see Fig. S1 and Vaccination section below.

We used the age-specific contact matrix \mathcal{M} for the US given in [18] and corrected for reciprocity. We assumed a baseline $R_0 = 3$ in absence of any social distancing interventions. To simulate social distancing interventions, we modified the matrices given in [18] (matrices corresponding to contacts at “home”, “work”, “other locations” and “school”) according to table S3 to obtain an effective reproduction number $R_{\text{eff}} = 1.2, 1, 4$, or 1.7 (assuming 10% pre-existing immunity). We used previously reported age-specific estimates of the severity of infections that

require hospitalization and critical care given in [42] and computed the number of hospitalizations leading to death using the rates given by [43]. These reports have different age brackets than those we utilize in our model, so we combined the brackets according to the proportion of the population in each bracket (e.g., for the oldest group in our model, ≥ 75 , we used a weighted average of the rates in [42] according to the relative percentages of the US population aged 75–80 and ≥ 80). Once hospitalized, individuals are assumed no longer infectious. Table S2 summarizes the parameter values, ranges, and sources for the model.

Simulations were run with initial conditions set to a 10% of the population with pre-existing immunity, distributed proportionally to population size (pro-rata) and disease severity, respectively (additional scenario, 20%, see Sensitivity Analysis). In addition, simulations were run with 1,000 infections initially, distributed among the infectious symptomatic and asymptomatic infectious compartments (compartments A_{ij} , $A_{V,ij}$, I_{ij} , $I_{V,ij}$, H_{ij} , $H_{V,ij}$, C_{ij} and $C_{V,ij}$).

Vaccination

Following the ideas of Halloran et al. [26], we assumed a leaky vaccine (that is, a vaccine that confers partial protection to all the vaccinees) that can have three effects on the vaccinated individuals. First, the vaccine can reduce the probability of acquiring a SARS-CoV-2 infection, (we denote this effect by VE_{SUS}). Second, the vaccine can also potentially reduce the probability of developing COVID-19 symptoms conditioned upon infection (referred to as VE_{SYMP} below), or third, reduce the infectiousness of vaccinated individuals (referred to as VE_I below), Fig. S2B. There is a multiplicative relationship between VE_{DIS} , VE_{SUS} and VE_{SYMP} [65], so that

$$VE_{DIS} = 1 - (1 - VE_{SUS})(1 - VE_{SYMP}).$$

A vaccine highly efficacious against disease could be either mediated mainly by protecting vaccinated individuals against infection (high VE_{SUS}), or mainly by preventing them from developing symptoms once infected (high VE_{SYMP}), or a combination of both. A vaccine with

a high VE_{SUS} or a high VE_I (irrespective of VE_{SYMP}) would have a bigger effect on the transmission dynamics of SARS-CoV-2, resulting in a greater population impact than one mediated primarily by VE_{SYMP} . In fact, a vaccine mediated exclusively by VE_{SYMP} might have only a direct effect, protecting only those vaccinated (this would be the case if infected asymptomatic individuals are equally infectious as symptomatic individuals). Values for all the combinations of vaccine efficacy profiles considered can be found in Table S1.

For each vaccination coverage and strategy considered, we computed within each age-group the fraction of susceptible individuals among all those individuals in that group who could have sought the vaccine (susceptible, exposed, infected pre-symptomatic, infected asymptomatic, and recovered asymptomatic populations), and utilized that fraction as the fraction of people who were actually vaccinated in each age-group, while assuming that the remaining vaccine would be wasted. Because it is expected that vaccine supplies will ramp up considerably over the second half of 2021 and into 2022, we focused on the first few months of vaccine availability and set 6 months as our time horizon, both for the optimization and for the population impact.

Vaccination campaigns were modeled assuming 150,000 doses of vaccines delivered weekly, over the span of ~ 6 months (28 weeks). At this rate, 50% of the population can be vaccinated over this time period with a single dose (25% with two doses). We also analyzed alternative scenarios with 300,000 doses delivered weekly (corresponding to vaccinating 100% of the population with one dose over the same time period) and instantaneous vaccination (as a proxy for fast vaccination campaigns). We modeled the vaccination campaigns by vaccinating first all the age-groups receiving two doses and then those receiving one dose, starting always with the oldest age-group and moving sequentially in decreasing order across the vaccine groups. So for example, if a particular strategy allocates vaccine as follows: 10% adults 20–50 with one dose, 10% adults 50–65 with two doses, 15% adults 65–75 with one dose and 40% adults aged 75 and older with two doses, then the vaccination in our model goes as follows: 1) vaccinate 40% of

adults aged 75 and older with one dose for as many weeks as necessary, then repeat this again to vaccinate them with their second dose. 2) Then we will vaccinate 10% of the adults aged 50–65 with two doses (similarly to the previous steps, in two rounds). 3) Then we will vaccinate 15% of adults aged 65–75 with one dose and finally 4) we will vaccinate 10% of those aged 20–50 with a single dose. The equations for this model are given by

Unvaccinated:

$$\begin{aligned}
 \frac{dS_i}{dt} &= -\lambda S_i, \\
 \frac{dE_i}{dt} &= \lambda S_i - \gamma_E E_i, \\
 \frac{dA_i}{dt} &= (1 - k)\gamma_E E_i - \gamma_A A_i, \\
 \frac{dP_i}{dt} &= k\gamma_E E_i - \gamma_P P_i, \\
 \frac{dI_i}{dt} &= \gamma_P P_i - (1 - h)\gamma_I I_i - h(1 - c)\sigma I_i - hc\sigma I_i, \\
 \frac{dH_i}{dt} &= h(1 - c)\sigma I_i - \gamma_H H_i, \\
 \frac{dICU_i}{dt} &= hc\sigma I_i - \gamma_C ICU_i, \\
 \frac{dRA_i}{dt} &= \gamma_A A_i, \\
 \frac{dR_i}{dt} &= \gamma_I I_i, \\
 \frac{dRH_i}{dt} &= \gamma_H H_i, \\
 \frac{dRC_i}{dt} &= \gamma_C ICU_i,
 \end{aligned}$$

Vaccinated ($j = 1, 2$ denotes vaccination with one or two doses respectively):

$$\begin{aligned}
 \frac{dS_{ij}}{dt} &= -\theta_j \lambda S_{ij}, \\
 \frac{dE_{ij}}{dt} &= \theta_j \lambda S_{ij} - \gamma_E E_{ij}, \\
 \frac{dA_{ij}}{dt} &= (1 - k\phi_j) \gamma_E E_{ij} - \gamma_A A_{ij}, \\
 \frac{dP_{ij}}{dt} &= k\phi_j \gamma_E E_{ij} - \gamma_P P_{ij}, \\
 \frac{dI_{ij}}{dt} &= \gamma_P P_{ij} - (1 - h) \gamma_I I_{ij} - h(1 - c) \sigma I_{ij} - hc \sigma I_{ij}, \\
 \frac{dH_{ij}}{dt} &= h(1 - c) \sigma I_{ij} - \gamma_H H_{ij}, \\
 \frac{dICU_{ij}}{dt} &= hc \sigma I_{ij} - \gamma_C ICU_{ij}, \\
 \frac{dRA_{ij}}{dt} &= \gamma_A A_{ij}, \\
 \frac{dR_{ij}}{dt} &= \gamma_I I_{ij}, \\
 \frac{dRH_{ij}}{dt} &= \gamma_H H_{ij}, \\
 \frac{dRC_{ij}}{dt} &= \gamma_C ICU_{ij},
 \end{aligned}$$

where $\theta_1 = 1 - \text{VE}_{\text{SUS}_1}$, $\phi_1 = 1 - \text{VE}_{\text{SYMP}_1}$ and $\psi_1 = 1 - \text{VE}_{\text{I}_1}$ and $\theta_2 = 1 - \text{VE}_{\text{SUS}}$, $\phi_2 = 1 - \text{VE}_{\text{SYMP}}$ and $\psi_2 = 1 - \text{VE}_{\text{I}}$. The force of infection λ is given by

$$\lambda = \sum_{k=1}^{16} \beta \frac{\mathcal{M}}{N_k} \left[r_A (A_k + \psi_1 A_{k1} + \psi_2 A_{k2}) + r_P (P_k + \psi_1 P_{k1} + \psi_2 P_{k2}) + (I_k + \psi_1 I_{k1} + \psi_2 I_{k2}) \right].$$

where \mathcal{M} is the sum of the contact matrices given in [18], corrected for reciprocity and weighted by the multipliers given in table S3.

Optimization

Objective functions: We performed the optimization routine to minimize five different objective functions: cumulative number of infections, cumulative number of symptomatic infections, cumulative number of deaths, maximum number of hospitalizations not requiring intensive care,

and maximum number of hospitalizations requiring intensive care. For each of these, we ran the deterministic model for 6 months (our time horizon).

Optimization: Here we describe our optimization routine, adapted from our previous work [17]. We randomly selected 10,000 points on a coarse grid [66] of the unit simplex in the vaccination group space (the set of vectors (v_1, v_2, \dots, v_5) with non-negative entries such that $\sum_{i=1}^5 v_i = 1$). The grid was chosen so that the unit simplex was divided into 0.05 units and was computed in Sage [67]. For each point in the coarse grid, the five objective functions were evaluated. For each of these objective functions, we selected the best 25 decision variables obtained in the grid search, the pro-rata allocation vector, the high-risk allocation vector and an additional 25 decision variables sampled uniformly from the unit simplex [68], and used these 52 points as initial points for the Nelder-Mead minimizer implemented in SciPy [69, 70]. Full details of the optimization routine can be found in [17].

The optimization for each combination of parameters (vaccination coverage, values of different vaccine profiles, level of viral transmission, etc.) was run independently and with different random seeds. As a result, the optimal allocation strategies are not always monotonic functions of coverage. In addition, it is important to note that, because of the particular way of modeling the vaccination campaign, a particular allocation can in principle, avert fewer infections or deaths than allocations with less coverage. This is because in our model, as more vaccine is available, it is always distributed to older adults first. More coverage implies more time spent in the older adults vaccination group, who are those transmitting the least, hence retarding vaccinating to the younger age groups, who are those transmitting most.

Uncertainty analysis

We examined the uncertainty in the output measures (percentage of infections averted and percentage of deaths averted, etc.) arising from uncertainty surrounding the model parameters. The following model parameters were varied for this analysis: the duration of the latent period, the duration of the pre-symptomatic, symptomatic and asymptomatic infectious periods, the relative infectiousness of the pre-symptomatic infected individuals, and the proportion of infections that are asymptomatic. We sampled parameter sets from predetermined distributions as follows: for the duration of the latent period, the duration of the pre-symptomatic, symptomatic and asymptomatic infectious periods we sampled gamma distributions with means given in table S2. For the proportion of asymptomatic infections and the relative infectiousness of the pre-symptomatic individuals we used truncated normal distributions with means and ranges given in table S2. We then sampled 1000 parameter sets and evaluated all three strategies (*optimal*, *pro-rata* and *high-risk*) for each of those sets. We also ran the simulation in absence of vaccination. We then computed the outcomes of interest and removed the the top and bottom 2.5%. The shaded areas presented in the figures are the result of this analysis.